EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

The optimisation of non-invasive ventilation in amyotrophic lateral sclerosis: A systematic review

David O'Brien, Theocharis Stavroulakis, Susan Baxter, Paul Norman, Stephen Bianchi, Mark Elliott, Maxine Johnson, Mark Clowes, Aldara Garcia-Sánchez, Esther Hobson, Christopher McDermott

Please cite this article as: O'Brien D, Stavroulakis T, Baxter S, *et al*. The optimisation of non-invasive ventilation in amyotrophic lateral sclerosis: A systematic review. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.00261-2019).

The optimisation of non-invasive ventilation in amyotrophic lateral sclerosis: A systematic review

David O'Brien, University of Sheffield, UK. ORCID: 0000-0001-5507-5649

Theocharis Stavroulakis, University of Sheffield, UK. ORCID: 0000-0002-3535-7822

Susan Baxter, University of Sheffield, UK. ORCID: 0000-0002-6034-5495

Paul Norman, University of Sheffield, UK. ORCID: 0000-0002-5892-0470

Stephen Bianchi, Sheffield Teaching Hospitals NHS Foundation Trust, UK. ORCID: 0000-0002-4987-3545

Mark Elliott, Leads Teaching Hospitals NHS Trust, UK. ORCID: 0000-0002-9295-5781

Maxine Johnson, University of Sheffield, UK. ORCID: 0000-0003-0850-234X

Mark Clowes, University of Sheffield, UK. ORCID: 0000-0002-5582-9946

Aldara Garcia-Sánchez, Ramón y Cajal Hospital, Spain. ORCID: 0000-0002-2065-9326

* Esther Hobson, University of Sheffield, UK. ORCID: 0000-0002-8497-2338

* † Christopher McDermott, University of Sheffield, UK. ORCID: 0000-0002-1269-9053

* Joint senior authors

† Corresponding author

Correspondence to:

Professor Christopher J McDermott, Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield S10 2HQ, UK

c.j.mcdermott@sheffield.ac.uk

Take home message

We report a systematic review that identifies factors associated with the optimal initiation and ongoing monitoring of NIV in patients with ALS. We make recommendations to optimise the use of NIV in ALS to improve patient outcomes.

Abstract

Background

Non-invasive ventilation (NIV) prolongs survival and quality of life in amyotrophic lateral sclerosis (ALS); however, its benefits depend upon the optimisation of both ventilation and adherence. We aimed to identify factors associated with effective initiation and ongoing use of NIV in ALS to develop evidence-based guidance and identify areas for further research.

Methods

We searched eleven electronic databases (Jan 1998 – May 2018) for all types of quantitative and qualitative studies. Supplementary grey literature searches were conducted. Records were screened against eligibility criteria, data were extracted from included studies and risk of bias was assessed. We present findings using a narrative synthesis.

Results

We screened 2430 unique records and included 52 quantitative and 6 qualitative papers. Factors reported to be associated with NIV optimisation included: co-ordinated multidisciplinary care, place of initiation, selection of interfaces, ventilator modes and settings appropriate for the individual patient, and adequate secretion management. The literature indicated that patients with significant bulbar dysfunction can still derive considerable benefit from NIV if their needs are met. Research emphasises that obstructive airway events, mask leak and uncontrolled secretions should be addressed by adjustments to the interface and machine settings, and the concomitant use of cough augmentation.

Conclusion

This review highlights that NIV optimisation requires an individualised approach to respiratory management tailored to the differing needs of each patient. Ultimately this should lead to improved survival and quality of life. This review expands on recommendations in current international guidelines for NIV use in ALS and identifies areas for future research.

Background

In patients with amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND), hypoventilatory respiratory failure is the most common cause of death and respiratory morbidity is related to a poorer quality of life (1). Non-invasive ventilation (NIV) improves survival and quality of life for patients with ALS in respiratory failure by up to 18 months (2, 3). However, the success of NIV is related to its optimisation: the quality (ventilation) and quantity (adherence) of NIV received are prognostic factors in ALS (4).

If ventilation is not optimised the benefits are dramatically reduced: the one-year survival was 75% in ALS patients experiencing good correction of hypoxia on NIV, reducing to 43% in the absence of good correction (4). Therefore, the effectiveness of ventilation needs to be monitored, with adjustments made to address any issues and compensate for further disease progression. Adherence must also be optimised. Patients who could tolerate NIV for four hours per day demonstrated improved survival post-NIV initiation (14.2 months) relative to those who used it for less than four hours per day (7.0 months, $p=0.002$) or those who declined NIV (4.6 months, $p<0.001$) (5).

NIV is a complex intervention (6), the success of which is influenced by the interaction of multiple service, equipment, patient and carer factors. These may include: the service delivery model and process of NIV initiation; the choice of mask interface, ventilator mode and machine settings; and the presence of significant bulbar dysfunction. Guidelines from the National Institute for Health and Care Excellence (NICE) (7), European Federation of Neurological Societies (EFNS) (8) and American Academy of Neurology (AAN) (9) for the management of NIV in ALS reflect the lack of evidence on how best to address these factors and, consequently, practice varies between services (10). The aim of this systematic review was to identify factors associated with optimal NIV initiation and ongoing adherence and ventilation in ALS to develop evidence-based guidance and identify areas for further research.

Methods

Protocol

The review protocol was registered with the PROSPERO database (CRD42018094394) and was conducted in accordance with PRISMA reporting standards (see Appendix 1) (11).

Search strategy

Eleven electronic databases were searched (from Jan 1998 – May 2018, except where stated): MEDLINE via OvidSP, MEDLINE In-Process & Other Non-Indexed Citations & Epub Ahead of Print & MEDLINE ® without Revisions via OvidSP, EMBASE via OvidSP, CINAHL via EBSCO, PsycINFO via OvidSP, Cochrane Database of Systematic Reviews via The Cochrane Library (2005 – May 2018), Database of Abstracts of Reviews of Effects via The Cochrane Library (1998 – April 2015; archive only), Cochrane Central Register of Controlled Trials (CENTRAL) via The Cochrane Library, Health Technology Assessment Database via The Cochrane Library, Science Citation Index via Web of Science and Social Sciences Citation Index via Web of Science.

Supplementary searching techniques included handsearching of included studies' reference lists and grey literature searches using OpenGrey and websites of relevant organisations, including those of the Motor Neurone Disease Association (https://www.mndassociation.org), NICE (https://www.nice.org.uk) and NHS Evidence (https://www.evidence.nhs.uk).

Search terms involved a combination of MeSH subject headings (e.g. Motor Neuron Disease, Noninvasive Ventilation, Artificial Respiration) and free-text terms (e.g. ALS, NIV, respiratory failure), with the search strategy developed and led by an information specialist. Searches were limited to humans and English language. The search strategy for MEDLINE is provided in Appendix 2.

Study selection

Citations retrieved from electronic database searches were uploaded to EndNote (Version 7). Titles and abstracts were independently screened by two reviewers against the eligibility criteria (see Table 1); a third reviewer resolved any uncertainties. The level of agreement between the two reviewers regarding study inclusion was over 95%. Full texts were then obtained.

Table 1. Study eligibility criteria

Criterion	Eligibility criteria
***P**opulation*	Studies in patients with a diagnosis of ALS/MND, or their families and caregivers, or healthcare professionals involved in their care.
***I**ntervention*	Studies involving any form of long-term, domiciliary NIV, defined as ventilatory support administered via a removable mask/mouthpiece.
***C**omparator*	Studies with comparator and non-comparator designs.
***O**utcome*	Studies reporting any outcome related to the optimisation of NIV initiation, monitoring and ongoing care (e.g. oxygen and carbon dioxide saturations, patient adherence and quality of life metrics).
***S**tudy design*	Empirical quantitative* and qualitative studies published in English in the last 20 years.**

ALS, amyotrophic lateral sclerosis; MND, motor neuron disease; NIV, non-invasive ventilation

* A range of quantitative studies were eligible, including randomised controlled trials and other experimental designs; prospective, retrospective and cross-sectional observational studies; and, case studies.

** The review was restricted to studies published in the last 20 years to ensure findings are relevant to current practice and given potential changes in prognosis during this timeframe.

Data extraction

Data were extracted from included studies using a pre-piloted extraction form. We collected data on: first author, publication year, study design, sample size, population characteristics, data collection method, outcome measures, intervention characteristics, theoretical underpinning, summary of results and main author conclusions. The form was suitable for all types of quantitative study designs and was modified for qualitative studies. Extraction forms for each study were completed by one reviewer and verified by a second, as is recommended as an accepted minimum (12). Multiple citations from a single study were brought together into a single extraction where possible, to avoid double-counting data.

Risk of bias assessment

We assessed the risk of bias using the established hierarchy of evidence and checklists for each study type, where appropriate. For controlled studies, we considered sources of potential bias as recommended by Cochrane (13). For other quantitative studies, we used the National Institutes of Health checklists (14). For qualitative studies, the Critical Appraisals Skills Programme checklist was used (15). Due to significant between-study heterogeneity, risk of bias was not assessed across the cumulative evidence.

Synthesis

Study heterogeneity precluded the use of a meta-analysis. Quantitative data were synthesised using a narrative synthesis method. Themes reported in qualitative studies were integrated where they related to the quantitative findings. We brought together studies examining similar processes or reporting similar outcomes, identifying where data agreed and where it conflicted, and provide an indication of the volume and quality of the evidence.

Results

Study selection

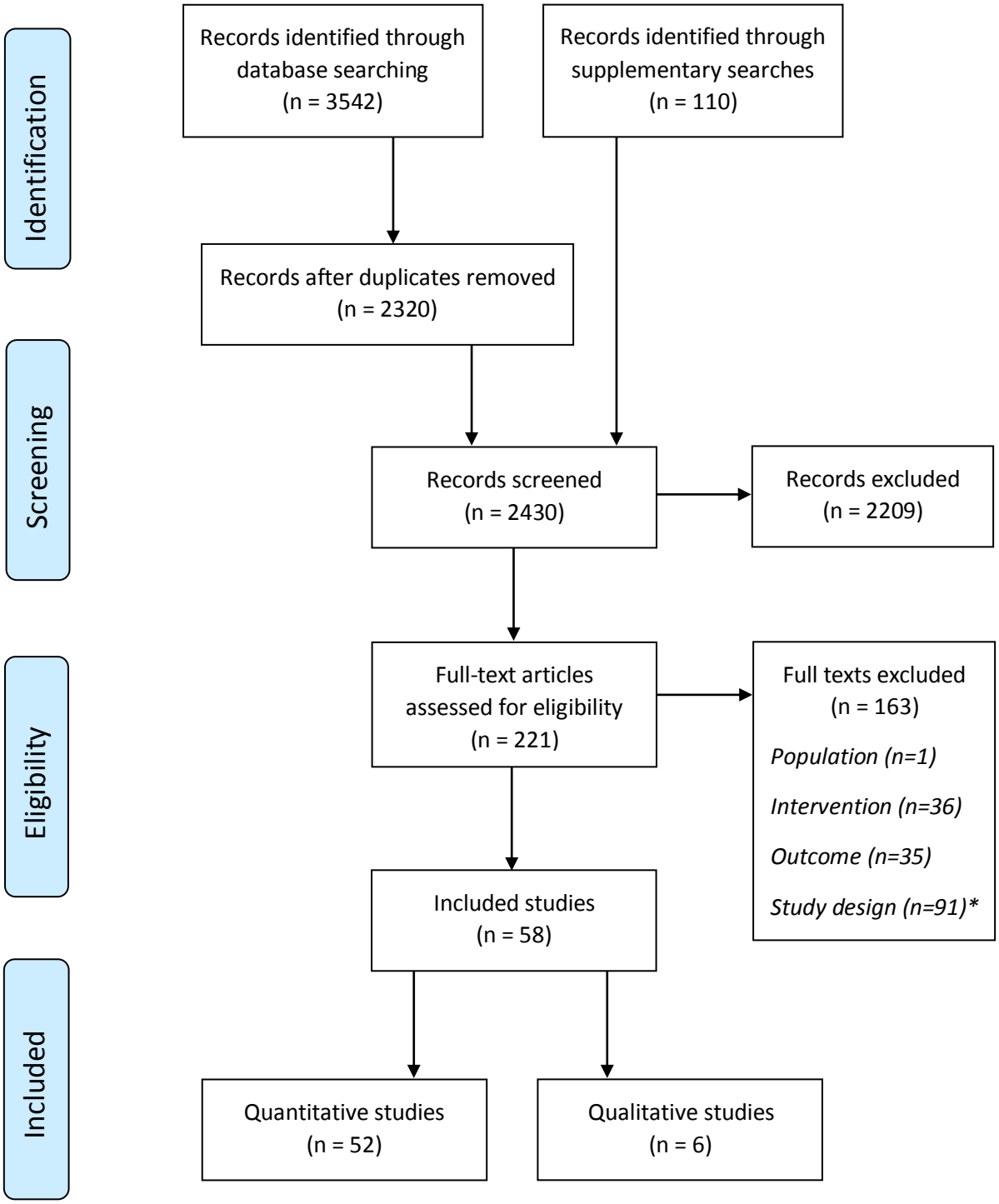
Of 2430 records screened, 221 documents were assessed at full-text level for eligibility, and 58 studies (52 quantitative and 6 qualitative) were included in the review (see Figure 1).

Study characteristics

The included studies involved a range of 1 – 474 participants (mean: 70.69). Five studies used an experimental design: two randomised controlled trials (RCT) (3, 16), two randomised crossover studies (17, 18) and one quasi-randomised controlled trial (19). The remaining quantitative studies were observational: 13 prospective, 16 retrospective, seven cross-sectional and 11 case studies. Six qualitative studies were also included. See Appendix 3 for the characteristics of included studies.

The included RCTs were found to be at a low risk of bias, while the other three experimental designs had a higher risk of bias, due to issues including: unclear random allocation method and reporting bias. The observational studies were all considered to be at higher risk of bias, although some provided more robust evidence than others; for example, seven included studies used a prospective design with sample size greater than 30 and adequate control for confounding variables (20–26). Completed quality assessments for individual studies are available as Appendix 4.

Figure 1. PRISMA flow chart illustrating the study selection process



n, number of studies; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

* The majority of those excluded on study design were conference abstracts (n=80) for which no full text could be obtained.

Service factors that influence NIV optimisation

Service delivery model

Eight studies investigated the effects of a multidisciplinary team approach to ALS care on NIV usage: one prospective (27), one retrospective (28) and six cross-sectional studies (29–34). Evidence was found in all for a positive effect of multidisciplinary care on outcomes related to NIV usage, including access to NIV, patient acceptance and adherence. A prospective Italian study in 37 patients evaluated a complex intervention during the initial adaptation to NIV, involving a patient education session, intensive inpatient monitoring, and follow-up with adjustments made as necessary (27). Adherence above four hours per night was achieved in all 37 patients at discharge after a mean inpatient stay of 12 ±2 days. At one-year, 35 of 37 (95%) patients remained NIV-adherent. A retrospective before-and-after study in 77 participants observed an increase in NIV acceptance following the addition of a respiratory therapist to the ALS clinic (54% to 82%, p=0.007) (28). Adherence above four hours per day also increased (22% to 73%, p=0.027). Both studies failed to adequately control for confounding variables.

In an epidemiological study of 259 patients in Italy, NIV was more frequently initiated within tertiary ALS centres than general neurology clinics from 1995–2004 (37.2% vs. 8.8%, p=0.0001) (29). Seventy-six Italian respiratory centres were surveyed in another study: 90% used a multidisciplinary approach, involving close co-operation between respiratory and neurology physicians, physiotherapists and psychologists (31). High-referring centres more frequently reported good collaboration with neurologists than low-referring centres (45% vs. 23%, p=0.04). Response rates below 50% increase the risk of bias here. A survey of 11 Canadian ALS specialists cited effective co-ordination between respiratory and neurology services and the availability of respiratory specialists as contributors to good NIV adherence (30). A UK audit described the utility of joint respiratory and palliative multidisciplinary clinics for monitoring respiratory function, commencing NIV and discussing end-of-life care in six patients (34).

Place of initiation

Five studies examined the effects of place of NIV initiation: one RCT (16), one prospective before-and-after study (26), two cross-sectional studies (34, 35) and one qualitative study (36). Two studies evaluated a day case (outpatient) model of initiation (16, 26). An Italian RCT compared initiation as a day case (n=25) versus an overnight inpatient (n=25) (16). Similar rates of NIV adherence were observed during initiation (76% vs. 80%, p=0.733) and at three months (68% vs. 76%, p=0.529). Patient and healthcare professional satisfaction, respiratory function changes and symptom control were similar in both groups. An Australian centre compared a multi-day inpatient initiation (n=17) to a day case initiation (n=12) in a prospective before-and-after study (26). 'Suitable patients' were initiated as outpatients, highlighting a possible selection bias. Median waiting time for NIV initiation fell from 30 to 13.5 days (p<0.04), and adverse events (death or acute admission with respiratory failure) declined from four out of 17 (24%) to 0 out of 12 (0%), while daytime arterial CO_2 levels were equivalent. Median post-initiation survival was extended from 278 to 580 days (hazard ratio: 0.41, p=0.04).

An international survey of 186 ALS clinicians found that patients are admitted to hospital for initiation more often in Europe than the USA (16/39 [41.0%] vs. 0/57 [0%], p<0.001) (35). However, a UK audit described successful home initiation in six patients with the support of a specialist respiratory nurse (34). A qualitative study reported patient anxiety regarding hospital admission; this was a major barrier for one patient who eventually accepted a trial of NIV as a day case (36).

Equipment factors that influence NIV optimisation

Interface

Sixteen studies examined the effect of the interface on NIV optimisation: one RCT (3), one randomised crossover trial (18), three prospective cohorts (22, 37, 38), four retrospective cohorts (4, 39–41), one cross-sectional survey (30), four case reports (42–45) and two qualitative studies (46, 47). Interface intolerance was associated with poor adherence in two prospective studies (22, 37), one cross-sectional (30) and one case report (44). Commonly reported problems in two qualitative studies included reluctance to use the mask in company, interference with eating and communication, pressure sores, dry mouth, mask leak and claustrophobia, which may contribute to poor adherence (46, 47). Six studies identified interface-related causes for ineffective ventilation: mask leak in four studies (4, 18, 38, 41) and obstructive sleep apnoea (OSA) in two (39, 42). A retrospective analysis identified mask leak as a leading source of persistent nocturnal desaturations in 53% of cases in 82 patients studied (4). Optimisation of mask fitting successfully minimised leak in this study and a case report (4, 45). In a retrospective cohort, NIV-associated OSA was present in 19 of 93 (20.4%) patients using oronasal masks (39). A case report also described OSA induced by an oronasal mask (42). Both studies reported changing to a nasal mask with a chin strap to eliminate obstructive events. One higher-quality RCT (3), one retrospective cohort (40) and a case report (43) highlighted the value of daytime mouthpiece ventilation, which facilitates adjuvant cough augmentation to expectorate secretions, although this requires adequate bulbar function (3, 40, 43).

Ventilator type, mode and settings

Eighteen studies assessed the effect of ventilator type, mode or settings on NIV optimisation: one randomised crossover trial (17), two prospective (37, 38), six retrospective (2, 4, 39, 41, 48, 49), six case reports (42, 45, 50–53) and three qualitative studies (46, 54, 55). A retrospective multicentre cohort with adequate control for confounding variables reported effective ventilation at one-month in 45 of 62 (72.6%) patients using volume-preset (Vol-NIV) systems compared with 40 of 82 (48.8%) patients using pressure-preset (Pres-NIV) systems ($p<0.001$) (2). However, there were no survival differences between the two groups ($p=0.533$). In a retrospective study of 271 patients, average volume-assured pressure support (AVAPS) ventilation produced greater average tidal volumes than Pres-NIV (390 vs. 356mL, $p=0.007$) with similar usage (6.5 vs. 6.6h/day, $p=0.703$) (49). These findings are limited by the possibility of selection bias and the use of surrogate outcomes for ventilation (lung volumes) rather than alveolar gases. Three studies reported the effects of switching from Pres-NIV to Vol-NIV or vice-versa. Switching from Pres-NIV to Vol-NIV resolved OSA in one patient in a large retrospective study (48) and improved ventilation in another case (44). A case series described a switch from Vol-NIV to Pres-NIV (in the case of increased leak) and vice-versa (in the case of increased secretions), which corrected hypoxia and hypercapnia, and improved symptoms, respectively (51).

The need to make decisions on a case-by-case basis was also demonstrated in a randomised crossover trial of spontaneous (S) and spontaneous/timed (ST) NIV modes in 13 patients (17). The ST mode provided more effective ventilation overall in terms of mean overnight oxygen saturations (87% vs. 83%, $p<0.05$) and time spent with an overnight transcutaneous CO_2 >55 mmHg (0% vs. 20%, $p<0.05$); however, four patients (who could not be predicted from baseline

characteristics) displayed better ventilation outcomes on the S mode. Survival effects were not assessed, while the risk of bias was considered high due to the small sample size and non-reporting of randomisation processes. Two prospective studies from the same centre described intolerance of the ST mode in seven out of 35 (20%) patients (five with bulbar involvement) (37) and six out of 22 (27%) patients (four with bulbar involvement) (38), respectively, which improved upon switching to the S mode in all cases.

Low-quality evidence from three case reports suggested poor NIV adherence due to air-swallowing (53), excessively high airway pressures on Pres-NIV machines (50) and target tidal volumes on Vol-NIV systems (45). In the latter case, adherence improved when target tidal volumes were reduced from 8ml/kg to 6ml/kg. Three qualitative studies linked discomfort associated with air pressure to reduced adherence (46, 54, 55). Conversely, insufficient ventilation settings were associated with poor ventilation in 34.7% patients in one retrospective study (41). Three studies reported the benefit of increasing ventilator support to improve ventilation, by increasing inspiratory positive airway pressure (IPAP) in a retrospective cohort (4) and case report (45) and increasing target tidal volumes in another case report (51). Increasing expiratory positive airway pressure (EPAP) helped to eliminate OSA in three retrospective studies (4, 39, 48). Other successful measures found to improve ventilation are reported in Table 2. A flow chart summary can be found in Appendix 5.

Table 2. Troubleshooting: NIV problems and solutions

Problem	Solution	Level of evidence
Obstructive airway events	Increase EPAP	Three retrospective studies (4, 39, 48)
	Switch to an auto-titrating mode of NIV	Two retrospective studies (39, 48)
	Switch from an oronasal mask to a nasal mask with a chin strap	One retrospective study (39) and one case report (42)
	Reduce inspiratory time and reduce IPAP	One case report (42)
	Switch from Pres-NIV to Vol-NIV	One retrospective study (48)
Mask leak	Optimise mask fitting	One retrospective study (4) and one case report (45)
	Switch from Vol-NIV to Pres-NIV	One case report (51)
Hypoventilation	Increase IPAP (Pres-NIV machines)	One retrospective study (4) and one case report (45)
	Increase target tidal volumes (Vol-NIV machines)	One case report (51)

	Switch from Pres-NIV to Vol-NIV	One case report (44)
Auto-triggering patient-ventilator asynchrony	Trial an increase in minimum inspiratory time*	One case report (52)
Excess respiratory secretions	Use adjuvant cough-assist devices	Three retrospective studies (56–58) and two case reports (43, 44)
	Switch from Pres-NIV to Vol-NIV	One case report (51)
Excess oropharyngeal secretions	Subcutaneous glycopyrrolate infusion	One case report (59)

EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; Pres-NIV, pressure-preset non-invasive ventilation; Vol-NIV, volume-preset non-invasive ventilation

* Only after first ensuring that the mask and tubing are free from condensation, that unintentional leak is minimised, and that appropriate trigger and cycle sensitivities are set. Minimum inspiratory times may not be adaptable on some ventilators.

Adjuvant therapies

Seven studies described the use of adjuvant interventions: two prospective (27, 60), two retrospective (48, 61) and three case studies (44, 50, 62). Music-assisted relaxation was beneficial in supporting NIV transition within the first week in a prospective feasibility study of 15 patients (60); however, risk of bias was deemed high due to methodological flaws in participant selection, outcome measurement and statistical analysis. Successful use of a portable hand-held ventilator (Philips 'Vitabreath') in three patients was reported in a case series, although the authors indicated that patients may struggle with the pressure differences compared to their usual ventilators (62). Two studies examined the use of mandibular advancement devices in treating OSA and improving NIV adherence: one case report described its successful use (50) while a retrospective study found no benefit (48).

Secretion management

Nine studies examined the impact of controlling secretions on NIV optimisation: two prospective (24, 27), three retrospective (56–58), three case reports (43, 44, 59) and one qualitative study (46). An association between excess oropharyngeal or airway secretions and poor adherence was found in two prospective studies (24, 27) and one case report (59). One prospective study found that an absence of airway secretions was predictive of good adherence (odds ratio: 11.5 [1.3–98.4]), while the case report described an improvement in NIV usage (from <1h to 6–8h/night) following treatment with a subcutaneous glycopyrrolate infusion (59).

Five studies highlighted the role of cough augmentation in the active management of secretions: three retrospective studies (56–58) and two case reports (43, 44). A retrospective analysis of 474 patients found a significant improvement in survival between NIV users who also used daily cough-assist compared to those using NIV alone (median: 25.73 months vs. 15.00 months,

p<0.001) (58). Combined use of NIV and cough-assist was successful in avoiding tracheostomy in two retrospective studies of 101 patients each (56, 57) and resolving 43 out of 78 (55%) desaturation episodes (57).

Efficacy monitoring

Monitoring ventilation

Two retrospective studies reported that effective ventilation predicted survival (4, 48), while another retrospective study did not find the effectiveness of NIV to be a prognostic factor (2). In one study, only 40 of 82 (49%) patients were effectively ventilated at one-month (4). Importantly, one-year survival was 75% in those effectively ventilated at one-month, declining to 43% in those ineffectively ventilated (p=0.002). Remedial measures at one- and three-months corrected ventilation by month six in 12 (43%) patients and one-year mortality in this subgroup was similar to those effectively ventilated at one-month (four deaths vs. three, p=0.13). In 16 (57%) patients NIV was still inadequate at month six despite corrective measures. One-year mortality in this subgroup was significantly higher than in those effectively ventilated at one-month (seven deaths vs. three, p=0.002). Another study found ineffective ventilation in 73 of 179 (41%) patients at one-month, due to OSA in 49 cases (67%) (48). Individuals adequately ventilated at one-month, and those for whom OSA was successfully eliminated within the first month, experienced greater median survival (26 [13–45] months and 29 [20–53] months, respectively) than those who were inadequately ventilated at one-month due to uncorrected obstructive events (14 [7–27] months, p<0.05) or other causes (12 [6–23] months, p<0.05).

Two retrospective studies investigated the need for longitudinal adaptations to machine settings with disease progression (2, 61). Twenty-eight out of 36 (78%) patients required at least one upward change in pressure settings (61). In a two-centre comparison, ventilator setting changes were required more frequently in 82 patients using pressure-preset (Pres-NIV) than 62 using volume-preset (Vol-NIV) machines: 51% vs. 14% (p<0.001) (2). Of those ineffectively ventilated in the first month, effective ventilation was achieved after the first modification in 79% of the Vol-NIV group and 31% of the Pres-NIV group (p<0.001).

Monitoring adherence

Survival correlated with hours of NIV use in three papers: one prospective cohort (21) and two retrospective cohorts (5, 58). Seventeen studies reported NIV adherence rates: nine prospective (20–24, 27, 37, 38, 63)**,** seven retrospective (2, 4, 28, 48, 49, 61, 64) and one cross-sectional study (29). The proportion of patients achieving at least four hours of use per day ranged from 46–100%.

Telemonitoring

The costs of a home telemonitoring system were analysed in a quasi-randomised controlled trial of 39 patients, observing a 55% reduction in average total costs in patients with the telemonitoring system (€8908.6 ± 6552.7) versus those on standard care (€19664.9 ± 5256.5) due to reduced healthcare utilisation (19). However, this reduction did not reach statistical significance (p=0.058). The impact of the telemonitoring system on NIV efficacy or survival was not assessed. This trial was judged to be at high risk of bias due to a non-random allocation method and potential reporting bias.

Patient and carer factors that influence NIV optimisation

Bulbar dysfunction

Twenty-three studies investigated the effects of bulbar impairment on NIV optimisation: two RCTs (3, 16), ten prospective cohorts (20–25, 37, 38, 63, 65), six retrospective cohorts (40, 56–58, 64, 66), two cross-sectional studies (29, 30) and three case reports (43, 44, 67). Nineteen studies found an association between bulbar impairment and poorer adherence or ventilation, while four studies (including one RCT) identified no such association. In this RCT, bulbar-onset disease predicted greater NIV adherence (16); however, another RCT reported an average use per day of 9.3 hours in the more preserved bulbar function subgroup versus 3.8 hours in those with poor bulbar function (3). In two prospective studies of 71 and 73 participants with adequate control for confounding variables, those with more severe bulbar impairment had an increased risk of poor adherence: six-fold in one (odds ratio: 6.09 [1.18, 31.52]) (21) and eight-fold in another (odds ratio: 8.5 [1.6, 46.2]) (24). In the latter trial, bulbar-predominant patients were reported to need more intensive and prolonged monitoring at NIV onset to maximise adherence (24). In spite of this, one prospective cohort reported one-year adherence above four hours per day in 35 out of 37 (95%) patients who had undergone an intensive education and adaptation programme at initiation despite nine presenting severe bulbar involvement at initiation and 23 mild-moderate impairment (27).

Eighteen studies investigated survival or quality of life outcomes in patients with bulbar dysfunction using NIV. Fourteen studies found that bulbar patients derived some benefit from NIV: two RCTs (3, 16), six prospective (20, 21, 27, 37, 38, 65), five retrospective (5, 41, 58, 64, 68) and one cross-sectional study (29). Four studies reported no benefit: three retrospective (40, 56, 57) and one case study (67). Generally, the gains derived in bulbar patients were reduced compared with non-bulbar patients, as reflected in an RCT where a subgroup with poorer bulbar function experienced no survival gain despite some quality of life benefits (3). However, the trial was not powered for this subgroup analysis. Perhaps surprisingly, one retrospective study observed a median survival benefit from NIV of 13 months in all 219 patients, increasing to 19 months in 58 with bulbar-onset disease (68).

Patient and carer perceptions

The effect of patient and carer perceptions on the optimisation of NIV was examined in four qualitative studies, involving between five and 37 participants (46, 47, 54, 69). Adaptation to NIV takes time for many patients, beginning with familiarisation with the equipment (69). Some patients highlighted the importance of an initial trial period to gauge the positive effects of NIV (69). Determination and perseverance were required to optimise adherence, while accessible in-person or telephone support might be beneficial in overcoming early obstacles (46). Carers reported a lack of confidence in adjusting the machine (46), which lessened with increased familiarity (47). Sleep disturbance may occur in patients and carers due to the machine noise and having to make adjustments to the system (46, 54). A positive coping style and perceived need to engage with the treatment was related to better adherence, while feelings of hopelessness were associated with poor adherence (54). Hopelessness was observed to be modifiable and improvements positively influenced patients' attitudes to NIV.

Discussion

This review has highlighted the importance of optimising both adherence and ventilation to gain the full benefit from NIV for patients with ALS. Patients must receive effective routine services, which should also be highly adaptable and co-ordinated to support the most complex patients who require the greatest clinical input. We recommend that services should adopt a co-ordinated, multidisciplinary approach aligned with current guidelines (7–9), but go further to recommend the need for specific professionals (including respiratory specialists) to be involved early and throughout the disease course to optimise adherence and ventilation. This will allow barriers to successful NIV use to be addressed prior to NIV initiation. The key benefits of this set-up in optimising NIV use may be one explanation for why multidisciplinary care is associated with improved survival compared to non-specialist services (32, 70–73).

Current guidelines make no reference to place of initiation, leading to practice variation (7–9). Outpatient or domiciliary initiation may promote acclimatisation, minimise patient anxiety and reduce delays in commencing NIV. In patients with chronic respiratory failure, outpatient (74) and domiciliary initiation (75) have been comparable to inpatient models in terms of adherence and ventilation and more cost-effective. The American Academy for Sleep Medicine also suggest that inpatient initiation can be difficult to justify both medically and financially (76). The Medical Research Council advise that complex interventions such as NIV work best if tailored and evaluated according to local circumstances rather than being completely standardised (6). Therefore, we recommend that outpatient (and perhaps home) initiation should be considered as an effective alternative to inpatient initiation; however, there should be means for more complex patients (e.g. those with significant bulbar impairment) to receive greater attention, which could involve an inpatient stay and more intensive monitoring to optimise efficacy.

We have highlighted the importance of the mask interface in NIV success and recommend that interface selection and fitting should be optimised to minimise leak and maximise comfort. This might involve offering a variety of interfaces and providing alternatives as necessary. Particular interfaces will have key benefits in certain scenarios; for instance, switching from an oronasal mask to a nasal mask with a chin strap to address obstructive events and the use of a mouthpiece in patients with adequate bulbar function to allow for daytime use and adjuvant cough augmentation. A recent review highlighted the broad range of airway clearance techniques available, which may be adapted according to individual patient requirements (77). Secretion management via cough augmentation and various pharmacological methods should be optimised alongside NIV.

It remains unclear which initial ventilator types, modes and settings are optimal but what is very clear is that setting adjustments are often required to achieve success. Ventilator choice may be restricted within certain health services, while the potentially damaging effects of using a spontaneous mode in patients with progressive respiratory muscle weakness must be considered (76). Effective ventilation is likely to confer a survival advantage, so we recommend this should be a goal in the first few months post-initiation whilst maintaining the balance between effective adherence, ventilation and comfort. To achieve this, and in contrast with published guidance, which suggests reviewing patients every two to three months (7–9), we recommend reviewing patients in the first few days and weeks to screen for and identify causes of poor efficacy and adjust NIV settings accordingly as adjustments appear to prolong survival

(4, 48). Particular attention should be paid to patients at higher risk of difficulties. Clinicians should be vigilant in their assessment of the optimal interface and NIV settings over time, as they will likely need altering due to evolving bulbar dysfunction and gradual weakening of the respiratory muscles. The most appropriate tests to monitor ventilation remain unclear. A working group of ten European ventilation specialists recommended that more complex tests (e.g. polysomnography) could have utility in titrating parameters, troubleshooting for problems and monitoring efficacy in more complex patients, but simple oximetry and ventilator-recorded data may suffice in most cases (78); this would free up resources to focus on those with the most barriers to success. An RCT in patients using positive airway pressure for OSA found that use of a telemonitoring system that allowed clinicians to identify problems and make adjustments to the settings remotely significantly improved adherence versus those using standard care (79). A 2016 systematic review recommended that further evidence is needed to demonstrate the value of telemonitoring in ALS (80).

Currently there is a reluctance among some clinicians to offer NIV to patients with significant bulbar impairment (10) and current guidelines suggest that these patients should only receive a trial of NIV if they are likely to benefit from an improvement in sleep-related symptoms (7), or should instead be offered tracheostomy-assisted ventilation or palliative care (8). Whilst patients with bulbar dysfunction face greater barriers to NIV success, the evidence suggests that they may gain both symptom and survival benefit that could be at least equal to that of non-bulbar patients. This benefit depends on strategies to promote effective use; for example, attention to secretion management, interface optimisation, adequate initial acclimatisation and ongoing active management with vigilant monitoring and adjustments made as necessary. These complex patients derive the greatest benefit from a multidisciplinary approach (71).

Qualitative studies highlighted the need to identify and address the barriers to acceptance and adaptation of the patient and carer to life with NIV. However, there is a lack of evidence on interventions to support patients and carers. An ongoing RCT in patients with chronic obstructive pulmonary disease is evaluating the effects of counselling, relaxation, mindfulness-based exercises and neuropsychological rehabilitation on NIV acceptance and adherence (81). One included study suggested that an educational programme can have a significant impact on adherence (27), while another proposed offering psychological interventions where adherence is suboptimal (55).

Strengths and limitations of this review

This is a systematic examination of the evidence exploring the optimisation of NIV use in ALS. Due to the breadth of the review, reporting has been unable to examine each paper in depth. Studies identified were largely observational with a paucity of randomised controlled trials. Therefore, any conclusions drawn from this review must be interpreted in light of the limited high-quality evidence available. Furthermore, any evidence must be considered in the context of individual patient and service needs. RCT evidence is likely to remain rare in this patient group due to ethical issues and clinical heterogeneity. Nonetheless, the review findings may be used to inform the development of guidelines for optimising the ALS patient care pathway and highlight areas that warrant further research (see Table 3).

Conclusion

There is a substantial body of evidence related to the optimal care of ALS patients on NIV, considering service, equipment, patient and carer factors. Factors optimising care for all

patients include: effectively co-ordinated multidisciplinary care; careful selection of interfaces, ventilator modes and settings appropriate for the individual patient; adequate secretion control; and vigilant monitoring and adjustment of settings. Attention to the factors identified will enable the delivery of evidence-based NIV therapy, which should ultimately improve patients' survival and quality of life.

Acknowledgements

The study was funded by The National Institute for Health Research (NIHR), within the Research for Patient Benefit Programme (PB-PG-1216-20041) and supported by the NIHR Sheffield Biomedical Research Centre (IS-BRC-1215-20017). Esther Hobson is funded by the NIHR and Health Education England (Clinical Lectureship scheme). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS) or the Department of Health and Social Care.

Table 3. Evidence-based recommendations

Optimising factor	Recommendations for practice	Level of evidence	Recommendations for research
Multidisciplinary care	The use of multidisciplinary clinics leads to greater NIV uptake.	Eight studies: - One prospective cohort (27) - One retrospective before-and-after study (28) - Three cross-sectional surveys (30, 31, 33) - Two epidemiological studies (29, 32) - One audit (34)	To further characterise the impact of multidisciplinary care and the role of respiratory and speech therapy specialists in certain patients (e.g. those with severe bulbar impairment).
	The involvement of respiratory specialists promotes good adherence.	Three studies: - One retrospective before-and-after study (28) - One cross-sectional survey (30) - One audit (34)	
	Effective co-ordination between neurology and respiratory services leads to good usage.	Two cross-sectional surveys (30, 31)	
Place of initiation	Outpatient initiation of NIV is likely to be an effective, cost-effective and acceptable alternative to inpatient initiation.	Two studies: - One RCT (16) - One prospective before-and-after study (26)	To strengthen the evidence for the comparative efficacy of domiciliary versus hospital inpatient and outpatient initiation, and explore patient preference.
	Initiation at home may be an effective way for patients to acclimatise to the ventilator and interface.	One audit (34)	To assess the feasibility of managing the complexities of NIV initiation in a single outpatient session.
	More complex patients (e.g. those with severe bulbar impairment) might require greater attention, which could involve an inpatient stay and more intensive monitoring in the initial phases to optimise efficacy.	Expert opinion.*	
Interface	Interface selection and fitting should be aimed at	Six studies:	To explore the effect of different

	optimising adherence by maximising comfort to prevent interface-related intolerance.	- Two prospective cohorts (22, 37) - One cross-sectional survey (30) - One case report (44) - Two qualitative studies (46, 47)	interfaces on patient adherence and the effectiveness of ventilation. To investigate the optimal interface for patients with bulbar and/or facial muscle weakness.
	Interface selection and fitting should also be aimed at optimising ventilation with a particular focus on minimising unintentional air leak.	Four studies: - One randomised crossover trial (18) - One prospective cohort (38) - Two retrospective cohorts (4, 39)	
	Particular interfaces should be available to trial in certain scenarios, for example: - A mouthpiece for patients with adequate bulbar function to allow for convenient daytime ventilation and adjuvant cough augmentation.	Three studies: - One RCT (3) - One retrospective cohort (40) - One case report (43)	
	- Switching from an oronasal mask to a nasal mask with a chin strap in the presence of obstructive events on NIV.	Two studies: - One retrospective (39) - One case report (42)	
Machine type, mode and settings	The choice of NIV machine, mode and settings should be adjusted according to the clinical scenario; if an individual patient demonstrates poor ventilation or adherence not related to the interface, consider changing:		To compare the efficacy of the different NIV machine types (pressure, volume, AVAPS) and modes (spontaneous, timed, ST). To explore the potential utility of continuous positive airway pressure (CPAP) therapy in ALS patients with coexisting OSA.
	- Machine settings (see Table 2)	Six studies: - Three retrospective studies (4, 39, 48) - Three case reports (45, 51, 52)	
	- Machine mode	Three studies: - One randomised crossover trial (17) - Two prospective cohorts (37, 38)	To further validate the accuracy of data provided by ventilator software (e.g. tidal volumes, leak).
	- Machine type.	Three studies:	

		- One retrospective (48) - Two case reports (44, 51)	
Secretion management	Cough-assist machines for airway secretion clearance should be combined with NIV to maximise survival and quality of life benefits.	Five studies: - Three retrospective cohorts (56–58) - Two case reports (43, 44)	To compare the effectiveness and cost-effectiveness of the various manual and mechanical airway clearance techniques that may be used in ALS.
	Ensure optimal oropharyngeal secretion control prior to and during NIV use to promote effective ventilation and good adherence, through the use of various pharmacological and non-pharmacological methods.	Four studies: - Two prospective cohorts (21, 24) - One case report (59) - One qualitative study (46)	
Monitoring	Close monitoring of all patients in the first few days and weeks post-initiation.	Expert opinion.	To explore a large scale, multidisciplinary initiation programme involving education, adaptive measures and monitoring.
	Additional provision for those at higher risk of difficulties (e.g. patients with severe bulbar impairment).	Expert opinion.	To explore the most clinically- and cost-effective methods for monitoring the effectiveness of NIV.
	Monitoring to identify poor adherence and ineffective ventilation and the implementation of corrective measures that could extend survival.	Two retrospective studies (4, 48)	To explore the best methods for monitoring patients who are deteriorating on NIV.
	Vigilant assessment of the optimal interface and NIV settings over time in the context of evolving bulbar dysfunction and gradual weakening of the respiratory muscles.	Two retrospective studies (2, 61)	To further investigate the potential utility of telemonitoring of NIV in ALS and resolve the issues with current systems (e.g. system specification, pre-determined alerts and the delivery of a patient-specific action plan)
Patient and carer perceptions	Attention should be paid to psychosocial aspects of care for all patients initiating NIV and their caregivers.	Expert opinion.	To explore the effects of different psychological interventions on NIV acceptance and adherence in ALS.
	Psychological interventions may be helpful	One qualitative study (55)	

	where adherence is suboptimal.		
Bulbar impairment	Patients with significant bulbar dysfunction can still derive significant benefit from NIV if their needs are met.	14 studies: - Two RCTs (3, 16) - Six prospective cohorts (20, 21, 27, 37, 38, 65) - Five retrospective cohorts (5, 41, 58, 64, 68) - One cross-sectional study (29)	To further examine the effect of these recommended measures on the efficacy of NIV in patients with significant bulbar dysfunction.
	Measures that should be taken to promote effective NIV use in these patients include: - Multidisciplinary care - Effective secretion management - Optimisation of interface selection and fitting - Initial adaptation, which might involve more intensive inpatient initiation procedures than for those with better bulbar function - Vigilant monitoring and troubleshooting - Proactive management, including attention to the appropriate interface and machine settings over time	Expert opinion.	

ALS, amyotrophic lateral sclerosis; AVAPS, average volume-assured pressure support; NIV, non-invasive ventilation; OSA, obstructive sleep apnoea; RCT, randomised controlled trial; ST, spontaneous-timed (mode)

* Expert opinion: Conclusions drawn by the review authors in their interpretation of the evidence. Some of these conclusions are reflected in the discussion sections of included studies.

References

1. Rafiq MK, Proctor AR, McDermott CJ, Shaw PJ. Respiratory management of motor neurone disease: A review of current practice and new developments. Pract Neurol. 2012;12(3):166–76.

2. Sancho J, Servera E, Morelot-Panzini C, Salachas F, Similowski T, Gonzalez-Bermejo J. Non-invasive ventilation effectiveness and the effect of ventilatory mode on survival in ALS patients. Amyotroph Lateral Scler Front Degener. 2014;15(1–2):55–61.

3. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: A randomised controlled trial. Lancet Neurol. 2006;5(2):140–7.

4. Gonzalez-Bermejo J, Morelot-Panzini C, Arnol N, Meininger V, Kraoua S, Salachas F, et al. Prognostic value of efficiently correcting nocturnal desaturations after one month of non-invasive ventilation in amyotrophic lateral sclerosis: A retrospective monocentre observational cohort study. Amyotroph Lateral Scler Front Degener. 2013;14(5–6):373–9.

5. Kleopa KA, Sherman M, Neal B, Romano GJ, Heiman-Patterson T. Bipap improves survival and rate of pulmonary function decline in patients with ALS. J Neurol Sci. 1999;164(1):82–8.

6. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: The new Medical Research Council guidance. Int J Nurs Stud. 2013;50(5):587–92.

7. National Institute for Health and Care Excellence. Motor neurone disease: assessment and management (NICE guideline NG42) [Internet]. 2016. Available from: https://www.nice.org.uk/guidance/ng42/

8. Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, Van Damme P, et al. EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) - revised report of an EFNS task force. Eur J Neurol. 2012;19(3):360–75.

9. Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, et al. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Drug, nutritional, and respiratory therapies (an evidence-based review). Neurology. 2009;73(15):1218–26.

10. O'Neill CL, Williams TL, Peel ET, McDermott CJ, Shaw PJ, Gibson GJ, et al. Non-invasive ventilation in motor neuron disease: An update of current UK practice. J Neurol Neurosurg Psychiatry. 2012;83(4):371–6.

11. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Med [Internet]. 2009 Jul 21;6(7):e1000097. Available from: https://doi.org/10.1371/journal.pmed.1000097

12. Centre for Reviews and Dissemination [Internet]. York; 2008. Available from: www.crd.york.ac.uk/crdweb/

13. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011] [Internet]. The Cochrane Collaboration. 2011. Available from: www.handbook.cochrane.org

14. National Institutes of Health. Quality Assessment of Systematic Reviews and Meta-Analyses. 2014.

15. Critical Skills Appraisal Programme (CASP) Qualitative Research Checklist. Available from: https://casp-uk.net/wp-content/uploads/2018/03/CASP-Qualitative-Checklist-2018_fillable_form.pdf

16. Bertella E, Banfi P, Paneroni M, Grilli S, Bianchi L, Volpato E, et al. Early initiation of night-time NIV in an outpatient setting: a randomized non-inferiority study in ALS patients. Eur J Phys Rehabil Med. 2017;53(6):892–9.

17. Vrijsen B, Buyse B, Belge C, Vanpee G, Van Damme P, Testelmans D. Randomized cross-over trial of ventilator modes during non-invasive ventilation titration in amyotrophic lateral sclerosis. Respirology. 2017;22(6):1212–8.

18. Crescimanno G, Greco F, Arrisicato S, Morana N, Marrone O. Effects of positive end expiratory pressure administration during non-invasive ventilation in patients affected by amyotrophic lateral sclerosis: A randomized crossover study. Respirology. 2016;21(7):1307–13.

19. Lopes de Almeida JP, Pinto A, Pinto S, Ohana B, de Carvalho M. Economic cost of home-telemonitoring care for BiPAP-assisted ALS individuals. Amyotroph Lateral Scler. 2012;13(6):533–7.

20. Aboussouan LS, Khan SU, Banerjee M, Arroliga AC, Mitsumoto H. Objective measures of the efficacy of noninvasive positive-pressure ventilation in amyotrophic lateral sclerosis. Muscle Nerve. 2001;24(3):403–9.

21. Lo Coco D, Marchese S, Pesco MC, La Bella V, Piccoli F, Lo Coco A. Noninvasive positive-pressure ventilation in ALS: predictors of tolerance and survival. Neurology. 2006;67(5):761–5.

22. Martinez D, Sancho J, Servera E, Marin J. Tolerance of Volume Control Noninvasive Ventilation in Subjects With Amyotrophic Lateral Sclerosis. Respir Care. 2015;60(12):1765–71.

23. Mustfa N, Walsh E, Bryant V, Lyall RA, Addington-Hall J, Goldstein LH, et al. The effect of noninvasive ventilation on ALS patients and their caregivers. Neurology. 2006;66(8):1211–7.

24. Vandenberghe N, Vallet A-E, Petitjean T, Le Cam P, Peysson S, Guerin C, et al. Absence of airway secretion accumulation predicts tolerance of noninvasive ventilation in subjects with amyotrophic lateral sclerosis. Respir Care. 2013;58(9):1424–32.

25. Servera E, Sancho J, Bañuls P, Marín J. Bulbar impairment score predicts noninvasive volume-cycled ventilation failure during an acute lower respiratory tract infection in ALS. J Neurol Sci. 2015;358(1–2):87–91.

26. Sheers N, Berlowitz DJ, Rautela L, Batchelder I, Hopkinson K, Howard ME. Improved survival with an ambulatory model of non-invasive ventilation implementation in motor neuron disease. Amyotroph Lateral Scler Front Degener. 2014;15(3–4):180–4.

27. Volanti P, Cibella F, Sarvà M, Cicco D De, Spanevello A, Mora G, et al. Predictors of non-invasive ventilation tolerance in amyotrophic lateral sclerosis. J Neurol Sci. 2011;303(1–2):114–8.

28. Kareus SA, Kagebein S, Rudnicki SA. The importance of a respiratory therapist in the ALS clinic. Amyotroph Lateral Scler. 2008;9(3):173–6.

29. Chio A, Calvo A, Moglia C, Gamna F, Mattei A, Mazzini L, et al. Non-invasive ventilation in amyotrophic lateral sclerosis: a 10 year population based study. J Neurol Neurosurg Psychiatry. 2012;83(4):377–81.

30. Ritsma BR, Berger MJ, Charland DA, Khoury MA, Phillips JT, Quon MJ, et al. NIPPV: prevalence, approach and barriers to use at Canadian ALS centres. Can J Neurol Sci. 2010;37(1):54–60.

31. Vitacca M, Vianello A. Respiratory outcomes of patients with amyotrophic lateral sclerosis: an Italian nationwide survey. Respir Care. 2013;58(9):1433–41.

32. Chiò A, Bottacchi E, Buffa C, Mutani R, Mora G, PARALS. Positive effects of tertiary centres for amyotrophic lateral sclerosis on outcome and use of hospital facilities. J Neurol Neurosurg Psychiatry. 2006;77(8):948–50.

33. Chio A, Silani V. Amyotrophic lateral sclerosis care in Italy: a nationwide study in neurological centers. J Neurol Sci. 2001;191(1–2):145–50.

34. Nixon I, Popkiewicz F, Banerjee S, Vincent-Smith L, Oliver D. Using a joint approach to non-invasive ventilation in motor neurone disease. Eur J Palliat Care. 2015;22:182–4.

35. Heiman-Patterson TD, Cudkowicz ME, De Carvalho M, Genge A, Hardiman O, Jackson CE, et al. Understanding the use of NIV in ALS: results of an international ALS specialist survey. Amyotroph Lateral Scler Front Degener. 2018;19(5–6):331–41.

36. Martin NH, Lawrence V, Murray J, Janssen A, Higginson I, Lyall R, et al. Decision Making About Gastrostomy and Noninvasive Ventilation in Amyotrophic Lateral Sclerosis. Qual Health Res. 2016;26(10):1366–81.

37. Vrijsen B, Buyse B, Belge C, Robberecht W, Van Damme P, Decramer M, et al. Noninvasive ventilation improves sleep in amyotrophic lateral sclerosis: A prospective polysomnographic study. J Clin Sleep Med. 2015;11(5):559–66.

38. Vrijsen B, Testelmans D, Belge C, Vanpee G, Van Damme P, Buyse B. Patient-ventilator asynchrony, leaks and sleep in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2016;17(5–6):343–50.

39. Schellhas V, Glatz C, Beecken I, Okegwo A, Heidbreder A, Young P, et al. Upper airway obstruction induced by non-invasive ventilation using an oronasal interface. Sleep Breath. 2018;22(3):781–8.

40. Bedard M-E, McKim DA. Daytime Mouthpiece for Continuous Noninvasive Ventilation in Individuals With Amyotrophic Lateral Sclerosis. Respir Care. 2016;61(10):1341–8.

41. Boentert M, Brenscheidt I, Glatz C, Young P. Effects of non-invasive ventilation on objective sleep and nocturnal respiration in patients with amyotrophic lateral sclerosis. J Neurol. 2015;262(9):2073–82.

42. Vrijsen B, Buyse B, Belge C, Testelmans D. Upper airway obstruction during noninvasive ventilation induced by the use of an oronasal mask. J Clin Sleep Med. 2014;10(9):1033–5.

43. Agrafiotis M, Papanikolaou G, Hospital G, Tryfon S, Hospital G, Obstructive C, et al. Noninvasive ventilation via mouthpiece in a patient with amyotrophic lateral sclerosis: A method to avoid tracheostomy and improve cough efficacy. Pneumon. 2017;30(2):31–5.

44. Belchior I, Goncalves MR, Winck JC. Continuous noninvasive ventilation delivered by a novel total face mask: a case series report. Respir Care. 2012;57(3):449–53.

45. Diaz-Abad M, Brown JE. Use of volume-targeted non-invasive bilevel positive airway pressure ventilation in a patient with amyotrophic lateral sclerosis,. J Bras Pneumol. 2014;40(4):443–7.

46. Baxter SK, Baird WO, Thompson S, Bianchi SM, Walters SJ, Lee E, et al. The initiation of non-

invasive ventilation for patients with motor neuron disease: patient and carer perceptions of obstacles and outcomes. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(2):105–10.

47. Sundling I-M, Ekman S-L, Weinberg J, Klefbeck B. Patients' with ALS and caregivers' experiences of non-invasive home ventilation. Adv Physiother. 2009;11(3):114–20.

48. Georges M, Attali V, Golmard JL, Morélot-Panzini C, Crevier-Buchman L, Collet JM, et al. Reduced survival in patients with ALS with upper airway obstructive events on non-invasive ventilation. J Neurol Neurosurg Psychiatry. 2016;87(10):1045–50.

49. Nicholson TT, Smith SB, Siddique T, Sufit R, Ajroud-Driss S, Coleman JM, et al. Respiratory Pattern and Tidal Volumes Differ for Pressure Support and Volume-assured Pressure Support in Amyotrophic Lateral Sclerosis. Ann Am Thorac Soc. 2017;14(7):1139–46.

50. Veldhuis SKB, Doff MHJ, Stegenga B, Nieuwenhuis JA, Wijkstra PJ. Oral appliance to assist non-invasive ventilation in a patient with amyotrophic lateral sclerosis. Sleep Breath. 2015;19(1):61–3.

51. Park D. Application of different ventilator modes in patients with amyotrophic lateral sclerosis according to certain clinical situations: A Case Report. Medicine (Baltimore). 2017;96(34):e7899.

52. Hannan LM, Rautela L, Wilson DL, Berlowitz DJ, Howard ME. Altering ventilator inspiratory time can reduce autocycling during sleep. Sleep Med. 2015;16(10):1301–3.

53. Yamada S, Nishimiya J, Kurokawa K, Yuasa T, Masaka A. Bilevel nasal positive airway pressure and ballooning of the stomach. Chest. 2001;119(6):1965–6.

54. Ando H, Chakrabarti B, Angus RM, Cousins R, Thornton EW, Young CA. Experience of long-term use of non-invasive ventilation in motor neuron disease: an interpretative phenomenological analysis. BMJ Support Palliat Care. 2014;4(1):50–6.

55. Ando H, Williams C, Angus RM, Thornton EW, Chakrabarti B, Cousins R, et al. Why don't they accept non-invasive ventilation?: insight into the interpersonal perspectives of patients with motor neurone disease. Br J Health Psychol. 2015;20(2):341–59.

56. Bach JR. Amyotrophic lateral sclerosis: prolongation of life by noninvasive respiratory aids. Chest. 2002;122(1):92–8.

57. Bach JR, Bianchi C, Aufiero E. Oximetry and indications for tracheotomy for amyotrophic lateral sclerosis. Chest. 2004;126(5):1502–7.

58. Khamankar N, Coan G, Weaver B, Mitchell CS. Associative Increases in Amyotrophic Lateral Sclerosis Survival Duration With Non-invasive Ventilation Initiation and Usage Protocols. Front Neurol. 2018;9:578.

59. Cooper-Knock J, Ahmedzai SH, Shaw P. The use of subcutaneous glycopyrrolate in the management of sialorrhoea and facilitating the use of non-invasive ventilation in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2011;12(6):464–5.

60. Tamplin J, Baker F, Davies R, Bajo E, Bolger K, Sheers N, et al. Exploring the feasibility of a music-assisted relaxation intervention to assist with the initiation of non-invasive ventilation in people with Motor Neuron Disease. Music Med. 2017;9:86–97.

61. Gruis KL, Brown DL, Lisabeth LD, Zebarah VA, Chervin RD, Feldman EL. Longitudinal assessment of noninvasive positive pressure ventilation adjustments in ALS patients. J Neurol Sci. 2006;247(1):59–63.

62. Oliver D, Banerjee S, Vincent-Smith L, Kindred J, Martin K. The use of a hand held ventilator to supplement NIV for patients with ALS/MND with respiratory insufficiency. Amyotroph Lateral Scler Frontotemporal Degener. 2018;19(3–4):313–4.

63. Butz M, Wollinsky KH, Wiedemuth-Catrinescu U, Sperfeld A, Winter S, Mehrkens HH, et al. Longitudinal effects of noninvasive positive-pressure ventilation in patients with amyotrophic lateral sclerosis. Am J Phys Med Rehabil. 2003;82(8):597–604.

64. Farrero E, Prats E, Povedano M, Martinez-Matos JA, Manresa F, Escarrabill J. Survival in amyotrophic lateral sclerosis with home mechanical ventilation: the impact of systematic respiratory assessment and bulbar involvement. Chest. 2005;127(6):2132–8.

65. Bourke SC, Bullock RE, Williams TL, Shaw PJ, Gibson GJ. Noninvasive ventilation in ALS: indications and effect on quality of life. Neurology. 2003;61(2):171–7.

66. Jackson CE, Lovitt S, Gowda N, Anderson F, Miller RG. Factors correlated with NPPV use in ALS. Amyotroph Lateral Scler. 2006;7(2):80–5.

67. De Vito EL, Suarez AA, Monteiro SG. The use of full-setting non-invasive ventilation in the home care of people with amyotrophic lateral sclerosis-motor neuron disease with end-stage respiratory muscle failure: a case series. J Med Case Rep. 2012;6:42.

68. Berlowitz DJ, Howard ME, Jr JFF, Hoorn S Vander, Donoghue FJO, Westlake J, et al. Identifying who will benefit from non-invasive ventilation in amyotrophic lateral sclerosis / motor neurone disease in a clinical cohort. J Neurol Neurosurg Psychiatry. 2015;87:1–7.

69. Lemoignan J, Ells C. Amyotrophic lateral sclerosis and assisted ventilation: how patients decide. Palliat Support Care. 2010;8(2):207–13.

70. Aridegbe T, Kandler R, Walters SJ, Walsh T, Shaw PJ, McDermott CJ. The natural history of motor neuron disease: Assessing the impact of specialist care. Amyotroph Lateral Scler Front Degener. 2013;14(1):13–9.

71. Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996–2000. J Neurol Neurosurg Psychiatry. 2003;74(9):1258–61.

72. Rooney J, Byrne S, Heverin M, Tobin K, Dick A, Donaghy C, et al. A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland. J Neurol Neurosurg & Psychiatry. 2015;86(5):496–501.

73. Rodríguez de Rivera FJ, Oreja Guevara C, Sanz Gallego I, San José Valiente B, Santiago Recuerda A, Gómez Mendieta MA, et al. Outcome of patients with amyotrophic lateral sclerosis attending in a multidisciplinary care unit. Neurología. 2011;26(8):455–60.

74. Chatwin M, Nickol AH, Morrell MJ, Polkey MI, Simonds AK. Randomised trial of inpatient versus outpatient initiation of home mechanical ventilation in patients with nocturnal hypoventilation. Respir Med. 2008;102(11):1528–35.

75. Hazenberg A, Kerstjens HAM, Prins SCL, Vermeulen KM, Wijkstra PJ. Initiation of home mechanical ventilation at home: A randomised controlled trial of efficacy, feasibility and costs. Respir Med. 2014;108(9):1387–95.

76. Berry RB, Chediak A, Brown LK, Finder J, Gozal D, Iber C, et al. Best clinical practices for the sleep center adjustment of noninvasive positive pressure ventilation (NPPV) in stable chronic alveolar hypoventilation syndromes. J Clin Sleep Med. 2010;6(5):491–509.

77. Chatwin M, Toussaint M, Gonçalves MR, Sheers N, Mellies U, Gonzales-Bermejo J, et al.

Airway clearance techniques in neuromuscular disorders: A state of the art review. Respir Med [Internet]. 2018;136:98–110. Available from: https://doi.org/10.1016/j.rmed.2018.01.012

78. Janssens J-P, Borel J-C, Pépin J-L. Nocturnal monitoring of home non-invasive ventilation: the contribution of simple tools such as pulse oximetry, capnography, built-in ventilator software and autonomic markers of sleep fragmentation. Thorax. 2011 May 1;66(5):438–45.

79. Fox N, Hirsch-Allen AJ, Goodfellow E, Wenner J, Fleetham J, Ryan CF, et al. The impact of a telemedicine monitoring system on positive airway pressure adherence in patients with obstructive sleep apnea: a randomized controlled trial. Sleep. 2012;35(4):477–81.

80. Hobson E V, Baird WO, Cooper CL, Mawson S, Shaw PJ, Mcdermott CJ. Using technology to improve access to specialist care in amyotrophic lateral sclerosis: A systematic review. Amyotroph Lateral Scler Frontotemporal Degener. 2016;17(5–6):313–24.

81. Volpato E, Banfi P, Pagnini F. A psychological intervention to promote acceptance and adherence to non-invasive ventilation in people with chronic obstructive pulmonary disease: study protocol of a randomised controlled trial. Trials. 2017;18(1):59.

Appendices

Appendix 1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5–6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13–19

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14–15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

Appendix 2. MEDLINE search strategy

1 exp Amyotrophic Lateral Sclerosis/ or exp Motor Neuron Disease/
2 (moto* neuron* disease* or moto?neuron* disease* or moto?neuron* disorder* or amyotrophic lateral sclerosis or Lou Gehrig* or Charcot disease). mp
3 (ALS or MND).mp.
4 1 or 2 or 3
5 exp Respiration, Artificial/ or exp Noninvasive Ventilation/ or exp Positive-Pressure Respiration
6 exp Respiratory Insufficiency/
7 exp Hypoventilation
8 (non?invasive adj5 ventilat*).mp.
9 (mechanical ventilat* or assisted ventilat* or positive pressure* or bi?level positive airway* pressure* or bipap or pressure support).mp.
10 (volume-control* ventilat* or pressure-control* ventilat*).mp
11 (NIV or NIPPV).mp.
12 (respiratory failure or respiratory insufficiency or hypoventilat* or hypercapni*).mp
13 tracheotomy.mp or exp Tracheotomy/
14 tracheostomy.mp or exp Tracheostomy/
15 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 4 and 15
17 limit 16 to (English language and humans)

Appendix 3. Characteristics of included studies

First author [ref] Year Country	Design Sample size*	Study objective	Outcome measures	Main findings (related to NIV optimisation)
Aboussouan [20] 2001 USA	Prospective cohort n = 47	To determine whether NIV improves survival, quality of life, lung volumes, blood gases and respiratory muscle strength.	Pulmonary function tests (FVC, FEV_1); Survival; Quality of life Blood gases (PaO_2, $PaCO_2$)	Survival greater in patients using NIV above four hours per day. Bulbar dysfunction predictive of poor NIV usage (below four hours per day). Bulbar dysfunction not correlated with survival.
Agrafiotis [43] 2017 Greece	Case report n = 1	To describe the use of NIV delivered via a mouthpiece and cough augmentation to avoid tracheostomy.	Descriptive	Daytime mouthpiece ventilation obviates the need for tracheostomy. The benefits of mouthpiece NIV depend upon adequate bulbar function.
Ando [54] 2014 UK	Qualitative: semi-structured interviews and interpretative phenomenological analysis n = 5	To explore patient perceptions of NIV, their evolution over time and how these impact upon usage.	Patient perceptions and experiences; NIV usage (hours per day)	A positive coping style and hope lead to better adherence. Improvements in feelings of hopelessness positively influence attitude towards NIV. Hopelessness was found to be modifiable; hence, it may be responsive to psychological interventions.
Ando [55] 2015 UK	Qualitative: semi-structured interviews and interpretative phenomenological analysis n = 9	To understand why some patients decline or withdraw from NIV.	Patient perceptions and experiences	Threats to the self, a sense of losing control and negative perceptions of NIV might all contribute to a refusal to accept NIV.

Bach [56] 2002 USA	Retrospective cohort n = 101	To describe the use of NIV and MAC to prolong survival.	NIV use; Oximetry (SpO_2) Pulmonary function tests; Peak cough flows; Survival: time to tracheostomy/ death	Reduced peak cough flows (<160L/min), an inability to breath-stack and baseline SpO_2 <95% predict the failure of NIV/MAC and a need for tracheostomy.
Bach [57] 2004 USA	Retrospective cohort n = 101	To explore the use of oximetry to guide the use of NIV and tracheostomy.	Oximetry (SpO_2); Pulmonary function tests; Peak cough flows	The combined use of MAC with NIV can correct desaturations in patients able to breath-stack. The ability to breath-stack (and hence successful use of NIV/MAC) is dependent upon glottic function. Home oximetry can monitor the effectiveness of NIV/MAC. Persistent desaturation unresponsive to NIV/MAC indicates the need for tracheostomy.
Baxter [46] 2013 UK	Qualitative: semi-structured interviews with thematic analysis n = 37 (20 patients and 17 carers)	To examine the perceptions and experiences of patients with MND and their carers following the recommendation to use NIV.	NIV use per day; patient perceptions and experiences	Potential barriers to NIV use include: negative first impressions, lack of confidence, negative sensation of air pressure, sleep disturbances for patients and carers, and interface issues. A need to persevere and get used to the device is necessary to overcome barriers and reap the benefits.
Bedard [40] 2016 Canada	Retrospective cohort n = 37	To explore the use of daytime mouthpiece ventilation to supplement nocturnal mask ventilation.	Survival (time from mouthpiece initiation to tracheostomy or death); bulbar subscore of the ALSFRS-R; peak cough flows; pulmonary function tests	Mouthpiece NIV is a suitable alternative to tracheostomy in those requiring continuous ventilation. Effective mouthpiece use is predicted via a bulbar subscore of the ALSFRS of ≥6 and adequate peak cough flows.
Belchior [44]	Case series	To describe a case series of patients	NIV and mask use; Nasal bridge sore	The total face mask provided effective ventilation for patients previously intolerant of oronasal or nasal masks.

2012 Portugal	n = 3	intolerant to oronasal or nasal masks and well-adapted to the total face mask.	score; Carbon dioxide levels	Tolerance of the total face mask was good in all cases. One patient switched from pressure-preset to volume-preset NIV, which improved ventilation.
Berlowitz [69] 2016 Australia	Retrospective cohort n = 219	To determine the effect of NIV on survival and any differences across clinical phenotypes.	Tracheostomy-free survival; Pulmonary function tests (FVC, FEV_1, etc.)	Tracheostomy-free survival from symptom onset was greater in those treated with NIV (28 months) versus those untreated (15 months, p=0.001). Overall survival benefit conferred by NIV was 13 months, rising to 19 months in those with bulbar-onset ALS.
Bertella [16] 2017 Italy	Randomised controlled trial n = 50	To compare a day case model and multiday inpatient model of NIV initiation in terms of patient acceptance, adherence, patient and staff satisfaction, symptoms and respiratory function changes.	NIV acceptance and adherence; Patient and staff satisfaction; Pulmonary function tests; Blood gases	A day case model of NIV initiation was comparable to a multi-day inpatient model in terms of patient acceptance of NIV and adherence, patient and staff satisfaction and symptom control. Bulbar-onset patients had greater NIV acceptance and adherence.
Boentert [41] 2015 Germany	Retrospective cohort n = 65	To investigate the effects of NIV on sleep outcomes and nocturnal respiratory parameters.	Blood gases (SaO_2, $tcCO_2$, $paCO_2$); Apnoea-hypopnoea index	Insufficient ventilation settings and mask leak were related to ineffective ventilation. The need for machine setting changes was similar in those with or without bulbar impairment.
Bourke [65] 2003 UK	Prospective cohort n = 15	To establish the quality of life benefits related to NIV, the optimal criteria for NIV initiation and the effects of bulbar impairment on outcome.	Quality of life indices (e.g. SF36); Symptoms Pulmonary function tests (e.g. FVC); Sleep quality	Patients with moderate-severe bulbar dysfunction were more difficult to establish on NIV, derived fewer benefits and had reduced compliance. Orthopnoea was the best predictor of compliance and asymptomatic patients had worse compliance. Compliance better in younger patients with preserved upper limb function.

Bourke [3] 2006 UK	Randomised controlled trial n = 41	To assess the effect of NIV on quality of life and survival.	Quality of life indices (e.g. SF36); Survival; Blood gases	Survival and quality of life benefits in the NIV group vs. standard care in all patients and in the subgroup with better bulbar function In the subgroup with worse bulbar function, there were some quality of life benefits but no survival benefits. NIV use per day higher in the group with better bulbar function versus those with worse bulbar function.
Butz [63] 2003 Germany	Prospective cohort n = 25	To evaluate the duration of benefit on symptoms and quality of life derived from NIV.	Quality of life indices; Symptoms	Patients with bulbar-onset disease or secondary bulbar involvement were less likely to use NIV.
Chio [33] 2001 Italy	Cross-sectional survey n = 36 (centres)	To gather information on management of patients across various neurology centres.	Survey responses	Patients underwent NIV more often in large centres.
Chio [32] 2006 Italy	Epidemiological study: analysis of routinely collected data n = 221	To evaluate the effects of tertiary ALS centres on outcome and the use of hospital facilities.	Survival; Use of interventions (e.g. NIV, PEG); Hospital admissions	Patients attending general neurology clinics underwent NIV less often than those attending tertiary centres.
Chio [29] 2012 Italy	Epidemiological study: analysis of routinely collected data n = 259	To evaluate the clinical characteristics and outcome of NIV using data from a prospective population register.	Tracheostomy-free survival; Use of interventions (e.g. NIV, PEG)	Patients attendings tertiary centres were more likely to undergo NIV and survive longer than patients attending general neurology clinics. Post-NIV survival was longest in younger, married patients and those receiving enteral nutrition. Severe bulbar impairment is a poor prognostic indicator.
Cooper-Knock [59] 2011 UK	Case report n = 1	To report the use of subcutaneous glycopyrrolate as a treatment for excess saliva.	NIV use per day	Control of sialorrhoea via subcutaneous glycopyrrolate infusion led to improved NIV tolerance and nightly NIV use.

Crescimanno [18] 2016 Italy	Randomised crossover study n = 25	To evaluate the application of expiratory positive airway pressure (EPAP) on outcomes.	Gas exchange (O_2, CO_2); Sleep quality; Patient-ventilator asynchrony; Leak; Minute ventilation	The application of EPAP has no effect on gas exchange but leads to increased leak, more. auto-triggering asynchronies and poorer sleep quality.
De Vito [67] 2012 Argentina	Case series n = 3	To describe three cases of patients who became continuously dependent on NIV.	Descriptive	Continuous NIV use obviates the need for tracheostomy provided bulbar function is adequate. Patients with an unmeasurable FVC in their final months can continue to use NIV successfully.
Diaz-Abad [45] 2014 USA	Case report n = 1	To report the case of a patient with rapidly progressing respiratory failure treated with AVAPS-NIV.	Descriptive	Excessively high target tidal volumes may lead to poor tolerance, which improves when tidal volumes are reduced. Device-recorded data can be interrogated to monitor progression.
Farrero [64] 2005 Spain	Retrospective cohort n = 64	To analyse the impact of a protocol of early respiratory evaluation and bulbar impairment on survival in NIV-treated patients.	Survival; Tolerance of NIV > 1 hour;	Bulbar impairment was present in all patients intolerant to NIV at initiation. Bulbar impairment reduced the survival of patients after NIV initiation.
Georges [48] 2016 France	Retrospective cohort n = 179	To describe NIV failure due to upper airway obstructive events and the impact of these events on prognosis.	Survival; Device-recorded data (obstructive events, use, leak); Blood gases (e.g. nocturnal SpO_2, $PaCO_2$); Polysomnography	Obstructive events were present in 45% of patients after correction of leak, and responsible for two-thirds of cases of ineffective ventilation. Obstructive events are an independent prognostic factor Survival is prolonged in patients for whom obstructive events are corrected versus those in whom they remained uncorrected.

Gonzalez-Bermejo [4] 2013 France	Retrospective cohort n = 82	To investigate whether the quality of NIV received (as measured via nocturnal oxygen saturations) impacts upon survival.	Survival; Nocturnal oxygen saturations; NIV use; Blood gases; Device-recorded data; Symptoms	Half of all patients were ineffectively ventilated at one-month (as measured by nocturnal oxygen saturations). Patients with more desaturations at initiation were more difficult to achieve effective NIV in. The effectiveness of ventilation was a prognostic factor. Correction of poor ventilation at one-month improves survival.
Gruis [61] 2006 USA	Retrospective cohort n = 36	To explore the use of pressure settings in NIV and the need for setting changes over time	Pressure settings; Survival; NIV tolerance (use ≥ 4 hours per night)	Most patients need at least one upward change of pressure settings, mostly in the first year. Patients tolerating NIV more than four hours per day experienced greater survival.
Hannan [52] 2015 Australia	Case report n = 1	To report a case where altering the ventilator inspiratory time reduced auto-cycling asynchronies.	Descriptive	Auto-cycling asynchronies may be reduced by increasing the minimum ventilator inspiratory time after checking the mask/tubing for condensation, minimising unintentional leak and settings appropriate trigger/cycle sensitivities.
Heiman-Patterson [35] 2018 USA	Survey of ALS clinicians n = 186 (responding clinicians)	To characterize the clinical use of NIV among ALS specialists in the US and Europe (e.g. regarding NIV initiation, obstacles to use, preferred equipment, etc.)	Survey responses	Patients are admitted to hospital for NIV initiation more often in the UK than the US. Practice differences between European and US clinicians may be explained by differences in insurance regulations and national healthcare coverage.
Jackson [66] 2006 USA	Retrospective cohort n = 403	To identify factors that may be correlated with NIV use and reasons for the underutilization of this therapy.	Factors associated with NIV use	Factors associated with NIV use are symptomatic orthopnoea and dyspnoea, male sex, increased income and use of other interventions (e.g. gastrostomy, speech augmentation, riluzole, suction devices and cervical collars). Site of onset was correlated with NIV use.
Kareus [28]	Retrospective before-and-after	To assess the use of NIV before and after	NIV use; Survival	The addition of a respiratory therapist led to increased acceptance and usage of NIV.

2008 USA	study n = 77	the introduction of a respiratory therapist to the ALS clinic.		Bulbar-onset patients were less likely to accept NIV and use it for more than four hours per day.
Khamankar [58] 2018 USA	Retrospective review of records n = 474	To identify the optimal timing for NIV initiation and the survival benefits of combining NIV with cough assist.	Survival; NIV use; ALSFRS-R; % predicted FVC	An optimised NIV protocol (initiation at FVC ≥80% predicted value, usage >8 h/day and daily cough assist use) confers a median survival around double that of the current US protocol (initiation at FVC <50% predicted, use >4 h/day, no cough assist). There was a significant difference between NIV users who also used cough assist compared to those using NIV alone. Patients with bulbar-onset disease experienced reduced benefit from NIV and cough assist compared with spinal-onset patients.
Kleopa [5] 1999 USA	Retrospective cohort n = 122	To evaluate the effects of NIV on survival and pulmonary function decline.	Survival; FVC decline (%/month)	No survival differences were found between bulbar-onset and limb-onset in survival benefit if NIV was well-tolerated. Survival was proportional to the quantity of NIV use.
Lemoignan [70] 2010 Canada	Qualitative: semi-structured interviews with phenomenological analysis n = 9	To understand the experience of decision-making around assisted ventilation.	Patient perceptions and experiences	Adaptation to NIV is a lengthy process that involves gradual familiarisation with the equipment and its benefits. NIV was viewed as a means of providing symptom relief. A trial period may be necessary to confirm that NIV did in fact improve their symptoms before deciding to continue using it.
Lo Coco [21] 2006 Italy	Prospective cohort n = 71	To identify factors associated with NIV tolerance and survival and to investigate the effects of NIV on lung function.	Survival; NIV use; FVC (% decline)	Site of onset not related to survival post-NIV initiation. Patients using NIV greater than four hours per day survived an average of one year longer than those using it less than four hours per day. Patients with mild-moderate bulbar dysfunction more six times more likely to use NIV more than four hours per day than those with severe bulbar dysfunction.

Lopes de Almeida [19] 2012 Portugal	Quasi-randomised controlled trial n = 39	To compare the cost of telemonitoring of NIV to standard care.	Healthcare costs (e.g. cost of hospitalisations, appointments, transport, maintenance of equipment)	There was a reduction in the average healthcare costs in patients with the telemonitoring system versus those on standard care by more than half, due to reduced healthcare utilisation.
Martinez [22] 2015 Spain	Prospective cohort n = 87	To determine the tolerance of volume-preset NIV (Vol-NIV) and the presence of factors predicting tolerance.	NIV use; Blood gases; Oximetry; Pulmonary function tests; Peak cough flows	Patients experienced a high rate of Vol-NIV tolerance (>4h daily use): 92% at three months. Longer periods of overnight oxygen desaturations and reduced peak cough flows predicted intolerance. Bulbar function or site of onset were not predictive of NIV tolerance.
Martin [36] 2016 UK	Qualitative: interviews with thematic analysis n = 5 (healthcare professionals interviewed about NIV decision-making)	To investigate factors affecting decision-making about gastrostomy and NIV from the viewpoint of the healthcare staff supporting them.	Views of healthcare professionals	Patients were more likely to accept NIV when they perceived few burdens or could be reassured that burdens could be minimized. There was anxiety about the need to be admitted to hospital.
Mustfa [23] 2015 UK	Prospective cohort n = 39	To describe the effect of NIV on survival, cognition, and the quality of life of both patients and carers.	Survival Quality of life indices; Cognitive assessments; Blood gas; Pulmonary function tests	Patients with poorer bulbar function were more likely to decline NIV or demonstrate poor adherence.
Nicholson [49] 2017	Retrospective cohort n = 271	To compare the efficacy of the AVAPS and pressure-preset systems and explore	Device-recorded data (NIV use, tidal volumes, minute ventilation, %spontan	AVAPS resulted in larger tidal volumes and less rapid shallow breathing versus Pres-NIV. No differences in usage were found between the AVAPS and Pres-NIV groups.

USA		the use of device-recorded data to monitor NIV efficacy.	eous cycles/triggers)	
Nixon [34] 2015 UK	Clinical audit n = 6	To evaluate a joint clinic for palliative and respiratory care and assess adherence to national guidelines.	Patient demographics; Assessment for NIV and monitoring of use	Six patients were successfully initiated on NIV at home by a specialist respiratory nurse.
Oliver [62] 2018 UK	Feasibility study n = 3	To assess the acceptability and effectiveness of a handheld ventilator.	Patient opinions of the ventilator (acceptability, usefulness and effectiveness)	Patients found it easy to use and it helped them maintain their independence (e.g. away from home). There were problems in that the pressures were not the same as they received with their NIV machines.
Park [51] 2017 South Korea	Case series n = 3	To investigate the utility of volume- or pressure-preset NIV in certain clinical situations.	Descriptive	Vol-NIV may have an advantage over Pres-NIV when the inner diameter of the airway decreases because of increased sputum. Pres-NIV may be preferable if not enough tidal volume is delivered due to increased mask leak.
Ritsma [30] 2010 Canada	Cross-sectional survey n = 11 responding clinicians (from 11 different centres)	To evaluate Canadian ALS centres with respect to the prevalence of NIV and tracheostomy use, and the barriers to NIV utilisation.	Survey responses	The main barriers to NIV use were patient intolerance, lack of access to ventilation specialists, equipment cost, patient refusal, and lack of available NIV machines or caregiver support.
Sancho [2] 2014 Spain & France	Retrospective cohort (two-centre) n = 144	To compare the Vol-NIV and Pres-NIV systems in terms of effective ventilation, compliance, survival, gas exchange and clinical outcomes.	Survival; Oximetry; Blood gases NIV use; Ventilator parameters	Vol-NIV provided more effective ventilation in terms of overnight oxygen saturations, was more effective at relieving symptoms and required fewer adjustments. Survival and NIV use were similar between the groups.

Schellhas [39] 2018 Germany	Retrospective: analysis of clinical data n = 93	To investigate the effects of pressure settings on upper airway obstructive events for patients using oronasal masks.	Apnoea-hypopnoea index; Ventilator parameters; Gas exchange; Sleep stages	NIV-associated obstructive events were found in 20.3% patients using oronasal masks. Changes that led to reductions in obstructive events include: increases in expiratory positive airway pressure (EPAP), changing to a variable EPAP and switching from an oronasal to nasal mask.
Servera [25] 2015 Spain	Prospective cohort n = 63	To determine whether clinical or functional parameters can predict failure of NIV for the treatment of acute respiratory failure.	NIV success/ failure; Gas exchange	A Norris bulbar score < 12 may predict NIV failure. Peak cough flows were also lower in failure group.
Sheers [26] 2014 Australia	Prospective before-and-after study n = 41	To compare a multi-day inpatient NIV initiation to a day admission model of initiation in terms of: waiting time for NIV, inpatient length of stay, adverse events and survival.	Wait-listed time for NIV; Survival; Adverse events; Daytime and early-morning arterial CO_2	Waiting times for NIV reduced by more than half with the day admission model, and survival extended by more than double. No significant change in ventilation effectiveness between the groups.
Sundling [47] 2009 Sweden	Qualitative: interviews with qualitative content analysis n = 15	To describe the experiences of NIV of patients and their caregivers.	Patient and caregiver perceptions and experiences	Patients reported problems with the mask (e.g. pressure sores, reluctance to use the mask in company, interference with sleep and eating). There were concerns regarding a lack of knowledge of how to use the equipment that lessened with time.
Tamplin [60] 2017 Australia	Prospective cohort feasibility study n = 15	To test the effects of a music-assisted relaxation intervention on NIV uptake, adherence, anxiety	NIV use; Patient anxiety; Quality of life	Supporting NIV transition within the first seven days may be advantageous for long-term adherence. No effects on anxiety or quality of life were found.

		and quality of life.		
Vandenberghe [24] 2013 France	Prospective cohort n = 73	To determine whether clinical and pulmonary parameters at initiation play a role in NIV tolerance.	NIV use (tolerance)	The most important and significant predictive factors for good tolerance were absence of airway secretion accumulation prior to starting NIV and good bulbar function.
Veldhuis [50] 2015 The Netherlands	Case report n = 1	To describe the combined use of NIV with a mandibular advancement device.	Descriptive	There is efficacy in the use of mandibular advancement devices to relieve upper airway obstructive events. High inspiratory pressures were intolerable for the patient.
Vitacca [31] 2013 Italy	Cross-sectional survey n = 76 centres	To explore current practice in Italian ventilation centres for ALS patients.	Survey responses	High-referring centres more frequently reported excellent or good collaboration with neurologists. 90% of Italian centres used a multidisciplinary approach.
Volanti [27] 2011 Italy	Prospective cohort n = 37	To evaluate the effect of a comprehensive NIV adaptation programme on patient adherence.	NIV use (tolerance; Setting changes; Survival	An intensive educational training and adaptation on non-invasive ventilation, when performed in a hospital multidisciplinary setting, increases compliance and tolerance over time, even in those patients with severe bulbar impairment.
Vrijsen [42] 2014 Belgium	Case report n = 1	To report a case of obstructive events in the upper airways, possibly induced by the use of an oronasal mask.	Descriptive	The use of an oronasal mask induced backward movement of the tongue during NIV use, causing upper airway obstruction. Switching to a nasal mask, reducing the inspiratory positive airway pressure (IPAP) and increasing the backup rate remedied the obstructive events and improved CO_2 levels.
Vrijsen [37] 2015	Prospective cohort n = 22	To evaluate the effects of NIV on sleep after meticulous titration via	Sleep parameters (e.g. sleep stages, arousal index); Gas exchange ($tcCO_2$,	The total cohort and the non-bulbar subgroup had improved sleep architecture and blood gases at one-month; improvements were less marked in the bulbar group. The ST mode was intolerable in seven patients, who were

Belgium		polysomnography.	$PaCO_2$, SpO_2); Quality of life indices	discharged on the spontaneous (S) mode.
Vrijsen [38] 2016 Belgium	Prospective cohort n = 35	To evaluate the prevalence of patient-ventilator asynchrony, leak and respiratory events during NIV and their impact on sleep.	Sleep parameters (e.g. sleep stages, arousal index); Gas exchange ($tcCO_2$, $PaCO_2$, SpO_2); Patient-ventilator interaction (asynchrony, leak, apnoea indices)	Although patient-ventilator asynchrony and leaks remain present after meticulous NIV titration, these events seem not to interfere with sleep. The ST mode was intolerable in seven patients who were instead discharged on the S mode.
Vrijsen [17] 2017 Belgium	Randomised crossover study n = 13	To compare the effects of a spontaneous (S) and spontaneous-timed (ST) mode of NIV on gas exchange, sleep architecture and patient-ventilator asynchronies.	Sleep parameters (e.g. sleep stages, arousal index); Gas exchange ($tcCO_2$, $PaCO_2$, SpO_2); Patient-ventilator interaction (asynchrony, leak, apnoea indices)	The ST mode was better on average in terms of gas exchange, sleep quality, apnoeas and asynchronies. Four patients had better outcomes on the S mode.
Yamada [53] 2001 Japan	Case report n = 1	To report a case of NIV causing gastric insufflation.	Descriptive	The ST mode and asynchrony may have contributed to gastric insufflation.

Sample size* - Where studies included patients without ALS, we report only the number of ALS patients, carers or healthcare professionals studied.

ALS, amyotrophic lateral sclerosis; ALSFRS-R, amyotrophic lateral sclerosis functional rating scale (revised); AVAPS, average volume-assured pressure support; CO_2, carbon dioxide; EPAP, expiratory positive airway pressure; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; h, hours; IPAP, inspiratory positive airway pressure; L, litres; MAC, mechanically-assisted cough; MND, motor neuron disease; n, number of participants; NIV, non-invasive ventilation; O_2, oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PEG, percutaneous endoscopic gastrostomy; Pres-NIV, pressure-preset non-invasive ventilation; S, spontaneous mode; SF36, 36-item short form survey; SpO_2, peripheral capillary oxygen saturation; ST, spontaneous-timed mode; $tcCO_2$, transcutaneous carbon dioxide; USA, United States of America; UK, United Kingdom; Vol-NIV, volume-preset non-invasive ventilation

Appendix 4. Study appraisal checklists

Experimental studies (n = 5)

First author & year	Potential for selection bias?		Potential for performance bias?	Potential for detection bias?	Potential for attrition bias?	Potential reporting bias?	Other sources of bias (comment)
	Random sequence generation.	Allocation concealment.	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcome data assessments	Selective reporting.	
Bertella 2017	Yes	Not possible	Not possible	Not possible	No	No	Complex intervention (hard to control all differences between day case and inpatient initiation procedures)
Bourke 2006	Yes	Yes	Not possible	Not possible	No	No	
Crescimanno 2016	Unclear	Unclear	Not possible	Not possible	No	Yes	No washout period
Lopes de Almeida 2012	Assigned according to residential area	Not possible	Not possible	Not possible	No	Yes	Complex data regarding effect on hospital costs versus total costs partially obscured in conclusions
Vrijsen 2017	Unclear	Not possible	Not possible	Unclear	No	No	No washout period

Cross-sectional studies (n = 7)

First author & year	1. Was the research question clearly stated?	2. Was the study population clearly specified and defined?	3. Was the participation rate of eligible persons at least 50%?	4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?	5. Was a sample size justification, power description, or variance and effect estimates provided?	6. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome?	7. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	8. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	9. Were the outcome assessors blinded to the exposure status of participants?	10. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
Chio 2001	Y	Y	N 36 of 80 centres	N	N	N/A	N/A	Y	Not possible	Y
Chio 2006	Y	Y	Y	Y	Y	N	N/A	Y	Not possible	Y
Chio 2012	Y	Y	Y	Y	Y	N	Y	Y	Not possible	Y
Heiman-Patterson 2018	Y	Y	Unclear	Y	N	N/A	N/A	N/A	N/A	N/A

Nixon 2015	Y	Y	Y	Y	N/A	Y	N/A	N/A	N/A	N/A
Ritsma 2010	Y	Y	Unclear	Unclear	N	N/A	N/A	N/A	N/A	N/A
Vitacca 2013	Y	Y	N	Y	N	N/A	N/A	N/A	N/A	N/A

Prospective cohort studies (n = 13)

First author & year	1. Was the study question or objective clearly stated?	2. Were eligibility/selection criteria for the study population pre-specified and clearly described?	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	4. Were all eligible participants that met the pre-specified entry criteria enrolled?	5. Was the sample size sufficiently large to provide confidence in the findings?	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	7. Were the outcome measures pre-specified, clearly defined, valid, reliable, and assessed consistently across all study participants?	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?
Aboussouan 2001	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N/A	N/A
Bourke 2003	Y	Y	Y	Y	Y	Y	Y	Unclear	Y	Y	N/A	N/A
Butz 2003	Y	Y	Y	Y	Unclear	Y	Y	N	Y	Y	N/A	N/A

Lo Coco 2006	Y	Y	Y	Y	Y	Y	Y	Unclear	Y	Y	N/A	N/A
Martinez 2015	Y	Y	Y	Unclear	Y	Unclear	Y	Unclear	N	Y	N/A	N/A
Mustfa 2006	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N/A	N/A
Servera 2015	Y	Y	Unclear	Y	Y	Unclear	Y	N	Y	Y	N/A	N/A
Sheers 2014	Y	Y	Y	Unclear	Y	Y	Y	Not possible	Unclear	Y	N/A	Y
Tamplin 2017	Y	N	Y	N	Y	Unclear	N	N	Y	N	N	Unclear
Vandenberghe 2013	Y	Y	Y	Y	Y	Y	Y	Unclear	N	Y	N/A	Unclear
Volanti 2011	Y	Y	Y	Y	Y	Y	Y	Not possible	Y	N	N/A	Unclear
Vrijsen 2015	Y	Y	Y	Y	Unclear	Y	Y	N	Y	N	N/A	N/A
Vrijsen 2016	Y	Y	Y	Unclear	Y	Y	Y	Unclear	Unclear	Y	N/A	Unclear

Retrospective studies (n = 16)

First author & year	1. Well-defined, clearly articulated research questions	2. Sampling questions considered *a priori?*	3. Operationalize variables included in retrospective chart review	4. Train and monitor data abstractors	5. Develop and use standardized data abstraction forms	6. Create a data abstraction procedure manual	7. Develop explicit inclusion and exclusion criteria	8. Address inter-rater and intra-rater reliability	9. Conduct a pilot test	10. Address confidentiality and ethical considerations
Bach 2002	Y	N	Not reported	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Bach 2004	Y	N	Not reported	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Bedard 2016	Y	N	Y	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Berlowitz 2016	Y	N	Not reported	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Boentert 2015	N	N	Not reported	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Farrero 2005	Y	N	Not reported	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Georges 2016	Y	N	Not reported	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Gonzalez-Bermejo 2013	Y	N	Y	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Gruis 2006	Y	N	Not reported	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Jackson 2006	Y	N	Not reported	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Kareus 2008	Y	N	Not reported	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported

Khamankar 2018	Y	N	Not reported	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Kleopa 1999	Y	N	Y	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Nicholson 2017	Y	N	Y	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Sancho 2014	Y	N	Not reported	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported
Schellhas 2018	Y	N	Not reported	Not reported	Not reported	Not reported	Y	Not reported	Not reported	Not reported

Qualitative studies (n = 6)

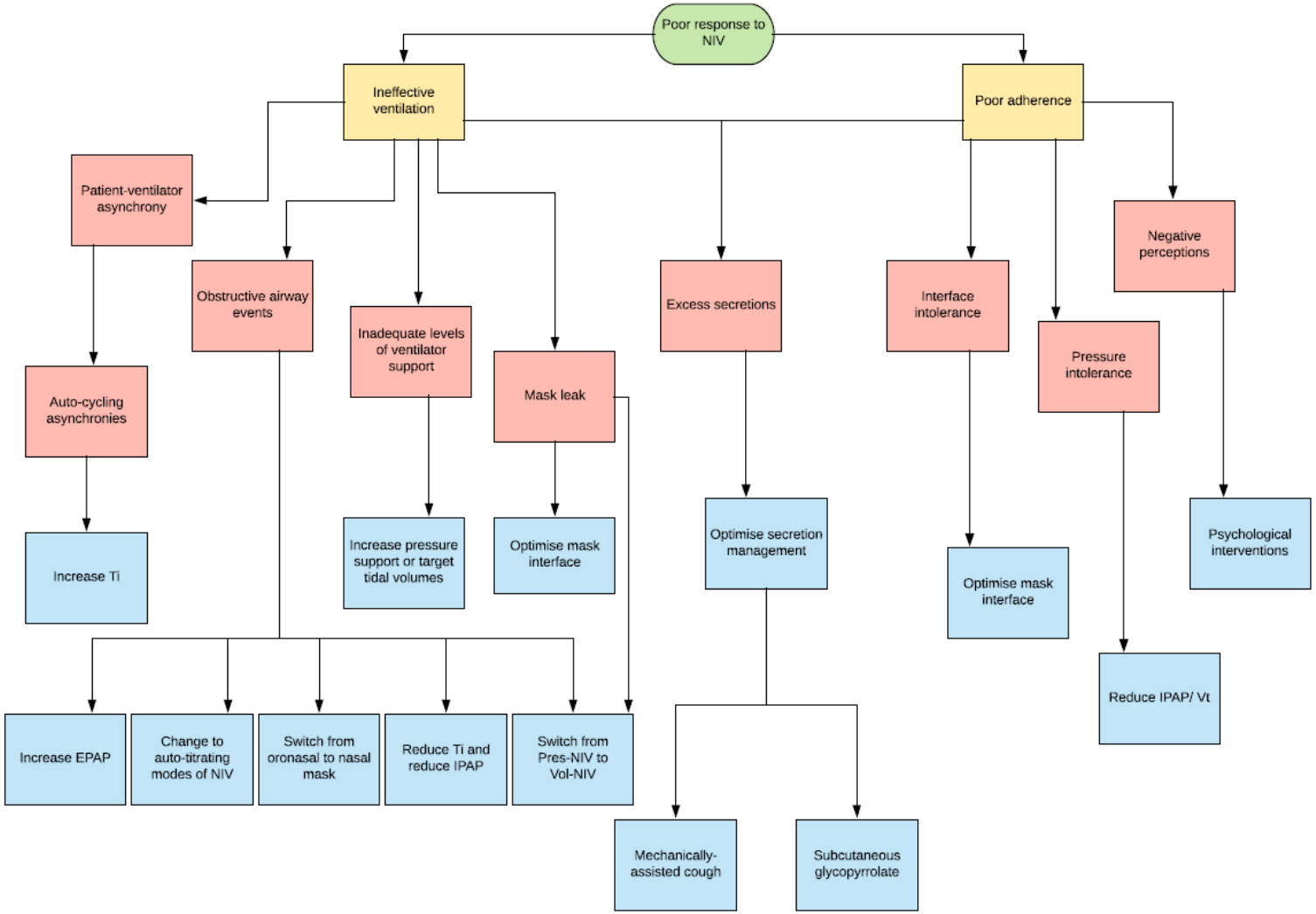
First author & year	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Ando 2014	Y	Y	Y	CT	Y	N	Y	CT	Y	Y
Ando 2015	Y	Y	CT	Y	Y	Y	Y	Y	Y	Y
Baxter 2013	Y	Y	CT	Y	Y	N	Y	Y	Y	Y
Lemoignan 2010	Y	Y	Y	CT	Y	Y	Y	Y	Y	Y
Martin 2016	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Sundling 2009	Y	Y	Y	CT	Y	Y	Y	Y	Y	Y

For each, Yes, Can't Tell or No

1. Was there a clear statement of the aims of the research? (what was the goal of the research; why it was thought important; its relevance)
2. Is a qualitative methodology appropriate? (If the research seeks to interpret or illuminate the actions and/or subjective experiences of research participants; Is qualitative research the right methodology for addressing the research goal)

3. Was the research design appropriate to address the aims of the research? (if the researcher has justified the research design, e.g. have they discussed how they decided which method to use)
4. Was the recruitment strategy appropriate to the aims of the research? (If the researcher has explained how the participants were selected; If they explained why the participants they selected were the most appropriate to provide access to the type of knowledge sought by the study; If there are any discussions around recruitment, e.g. why some people chose not to take part)
5. Was the data collected in a way that addressed the research issue? If the setting for the data collection was justified; If it is clear how data were collected (e.g. focus group, semi-structured interview etc.); If the researcher has justified the methods chosen; If the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews are conducted, or did they use a topic guide); If methods were modified during the study. If so, has the researcher explained how and why; If the form of data is clear (e.g. tape recordings, video material, notes etc.); If the researcher has discussed saturation of data
6. Has the relationship between researcher and participants been adequately considered? (If the researcher critically examined their own role, potential bias and influence during (a) formulation of the research questions (b) data collection, including sample recruitment and choice of location; How the researcher responded to events during the study and whether they considered the implications of any changes in the research design
7. Have ethical issues been taken into consideration? (If there are sufficient details of how the research was explained to participants for the reader to assess whether ethical standards were maintained; If the researcher has discussed issues raised by the study (e.g. issues around informed consent or confidentiality or how they have handled the effects of the study on the participants during and after the study; If approval has been sought from the ethics committee
8. Was the data analysis sufficiently rigorous? (If there is an in-depth description of the analysis process; If thematic analysis is used. If so, is it clear how the categories/themes were derived from the data; Whether the researcher explains how the data presented were selected from the original sample to demonstrate the analysis process; If sufficient data are presented to support the findings; To what extent contradictory data are taken into account; Whether the researcher critically examined their own role, potential bias and influence during analysis and selection of data for presentation
9. Is there a clear statement of findings? (If the findings are explicit; If there is adequate discussion of the evidence both for and against the researcher's arguments; If the researcher has discussed the credibility of their findings (e.g. triangulation, respondent validation, more than one analyst); If the findings are discussed in relation to the original research question
10. How valuable is the research? (if the researcher discusses the contribution the study makes to existing knowledge or understanding (e.g. do they consider the findings in relation to current practice or policy, or relevant research-based literature; If they identify new areas where research is necessary; If the researchers have discussed whether or how the findings can be transferred to other populations or considered other ways the research may be used

Appendix 5. Flow chart summary of troubleshooting measures



EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; NIV, non-invasive ventilation; Pres-NIV, pressure-preset non-invasive ventilation; T_i, inspiratory time; Vol-NIV; volume-preset non-invasive ventilation; V_t, target tidal volum