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Protocol Article

Outpatient versus inpatient initiation of home mechanical ventilation in patients with amyotrophic lateral sclerosis – a protocol for a randomised trial

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ABSTRACT

INTRODUCTION. In-home non-invasive ventilation (NIV) is associated with prolonged life and improved quality of life in patients with hypoventilation due to amyotrophic lateral sclerosis (ALS). The initiation of NIV is scheduled for a 1-2-night hospital stay. Telemedicine enables remote monitoring and adjustment of respiratory treatment. These possibilities should be examined to improve patients' experiences and adherence to treatment while freeing up resources in the healthcare system. We hypothesise that outpatient initiation of NIV combined with close telemonitoring in patients with ALS is non-inferior to standard initiation of NIV in adherence to treatment.

METHODS. This is a randomised, controlled, non-inferiority study. A total of 46 patients with ALS scheduled for initiation of NIV are randomised to start NIV either as an outpatient combined with close telemonitoring or during hospitalisation for 1-2 nights. The primary outcome is NIV adherence after three months, measured as minutes per day for the past seven days. Secondary outcomes are patient satisfaction with NIV treatment and its initiation after three months, assessed on a 1-5 rating scale.

CONCLUSIONS. The study is the first randomised, controlled study assessing the combination of outpatient initiation of NIV and close telemedical follow-up in patients with a progressive neuromuscular disease. The results may be applicable to other patient populations initiating NIV, e.g., patients with obesity hypoventilation syndrome.

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Patients with amyotrophic lateral sclerosis (ALS) develop chronic respiratory insufficiency due to progressive muscle weakness. Typically, nocturnal hypoventilation is first seen, followed by daytime hypoventilation as lung volume capacity decreases. Treatment with home non-invasive ventilation (NIV) may improve quality of life and is associated with prolonged life expectancy [1]. A retrospective study from 1999 showed that home NIV for a minimum of four hours/day increased survival compared with less than four hours among patients with ALS [2]. However, treatment adherence may be a challenge [3].

Patients with ALS and chronic respiratory insufficiency are typically admitted to the hospital for 1-2 nights to initiate home NIV treatment while being monitored. This includes cardiorespiratory and transcutaneous CO_2 ($tcCO_2$) monitoring during sleep as well as a capillary blood gas test (CBG) before and after sleep to adjust NIV settings. However, hospital admission is very resource-intensive, especially for this group of patients with limited remaining lifespans.

Telemedicine software solutions have enabled remote monitoring and adjustment of NIV treatment. Moreover, it may enable safe outpatient initiation of NIV in patients with a potential rapidly progressing neuromuscular disease.

This study is designed to assess the effect of outpatient NIV initiation combined with close telemedicine monitoring compared with conventional in-hospital initiation. We hypothesise that outpatient initiation of NIV combined with close telemedicine monitoring for patients with ALS is non-inferior to hospital-based initiation in terms of treatment adherence and patient-reported experience measures (PREMs).

METHODS

Study design

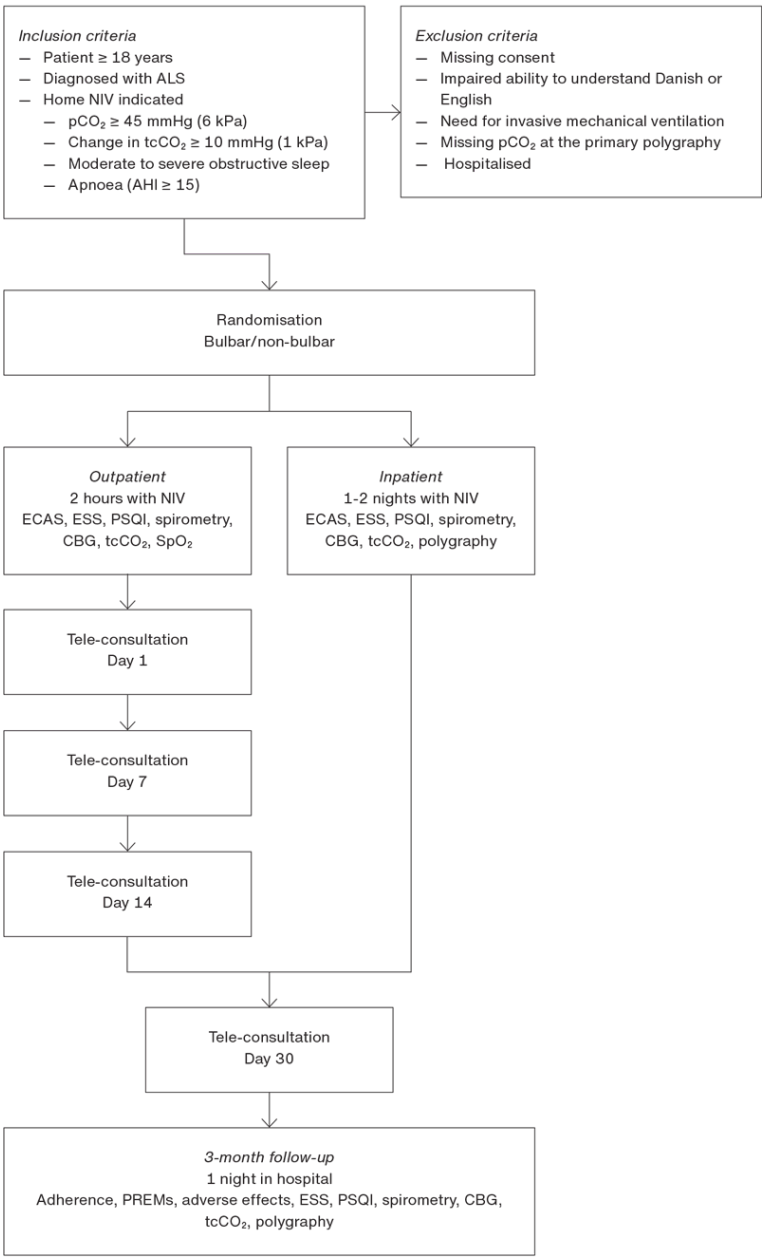
This ongoing investigator-initiated study (launched August 2023) is a stratified, randomised, controlled and assessor-blinded study.

Study population

The subjects for this study will be recruited at the Respiratory Center East in East Denmark.

Adult patients (≥ 18 years) diagnosed with ALS according to the Gold Coast criteria [4] and who meet one of three specified criteria for NIV treatment [5] (a modification of the Canadian guidelines [6]) are screened for inclusion (**Figure 1**). Study inclusion and exclusion criteria are listed in Figure 1.

FIGURE 1 Patient inclusion.



AHI = apnoea-hypopnoea index; ALS = amyotrophic lateral sclerosis; CBG = capillary blood gas test; ECAS = Edinburgh Cognitive and Behavioral ALS Screen; ESS = Epworth Sleepiness Scale; NIV = non-invasive ventilation; PREMs = patient-reported experience measures; PSQI = Pittsburgh Sleep Quality Index; SpO_2 = pulse oximetry; $tcCO_2$ = transcutaneous CO_2.

Recruitment

Patients who meet the inclusion criteria after diagnostic polygraphy and have no exclusion criteria will receive some brief initial information about the study. If they express interest, they will be provided with written materials and detailed oral information from a study investigator. After adequate time for consideration, they will be invited to sign an informed consent form.

Randomisation

Computer-generated randomisation is used with stratification for significant bulbar affection (Revised ALS

Functional Rating Scale (ALSFRS-R), bulbar sub score ≤ 9) [7] to ensure equal distribution of these patients across both groups.

Patients are allocated to either initiate NIV as an outpatient (intervention group) or as an inpatient (control group).

Randomisation is performed after written informed consent is obtained. Before randomisation, the patients are asked which group they would prefer and why.

Randomised patients who do not come for NIV initiation or are emergently admitted to the hospital prior to the start will be registered as dropouts and will be replaced.

Blinding

The investigator who assesses data for primary outcomes will be blinded, as he/she will not have access to patient-identifiable data but only to non-identifiable data, reading the telemedicine software AirView™, ResMed, Denmark. Due to the study setting, neither other healthcare professionals nor patients can be blinded.

Inpatient group

Currently, patients in East Denmark with ALS and chronic respiratory insufficiency with indication for home NIV are referred for hospitalisation for 1-2 nights to initiate NIV treatment at Respiratory Center East. **Table 1** outlines the approaches to initiating NIV.

TABLE 1 Description of suggested settings of the ventilator when initiating in-home non-invasive ventilation in patients with amyotrophic lateral sclerosis.

Theme	Suggested settings
Choice of mask	Nasal mask
	Full-face mask
NIV setting from start	S/T modus
	IPAP: 10 in the first few min., and then increased to 12 cmH_2O
	EPAP: 4-6, 6 cmH_2O if obstruction is detected in the diagnostic polygraphy
	Backup respiration rate: 12/min.
	Ti min and Ti max: usually 1.3-2.5 seconds, depending on comorbidity
	Ramp: off
	Rise time: 300-450 milliseconds, depending on the patient's response
	Trigger: start with medium
	Cycles: start with medium
Goal of Vt	7.8 ml/kg ideal weight, less Vt is accepted initially
Mask leak	Mask leak > 25 l/min., consider another mask or reduce IPAP
O_2	Patients receiving O_2 therapy will maintain their usual daytime flow rate during NIV
	O_2 will be initiated in patients not already on O_2 therapy if clinically indicated
Humidifier and heating tubes	The need for a humidifier and heated tubing will be evaluated

EPAP = expiratory positive airway pressure; IPAP = inspiratory positive airway pressure; NIV = non-invasive ventilation; S/T modus = spontaneous/timed modus; Ti max = maximum inspiration time; Ti min = minimum inspiration time; Vt = tidal volume.

Patients are monitored by respiratory polygraphy during NIV, with monitoring of the apnoea-hypopnoea index, respiratory rate, heart rate and body position, and tcCO2 and pCO_2 from CBG, daytime and morning. NIV settings are titrated by a trained nurse and the attending physician.

Outpatient group

Patients test the NIV treatment for a minimum of two hours while being monitored with pulse oximetry (SpO_2) and a $tcCO_2$ monitor using the same approach regarding settings as the standard group (Table 1). A CBG is performed before and after NIV testing. NIV settings are titrated as needed. Patients are discharged if the attending physician deems it justified.

Teleconsultation: Patients are contacted by telephone by a doctor one, seven and 14 days after NIV initiation. Information from participants and telemonitoring is assessed, and NIV settings are adjusted if indicated (Supplement 1). However, any modifications are at the discretion of the attending physician.

Both groups

All patients are offered a 24-hour telephone support line, and we encourage them to contact the department as needed. A pamphlet on the NIV is distributed.

Teleconsultation with standard questions combined with information from the telemonitoring is performed 30 days after initiation in both groups, which is in accordance with the current standard at the department, and NIV settings are adjusted if indicated.

Moreover, all patients are scheduled for a one-night stay at the hospital three months after initiation of NIV for assessment of the respiratory treatment by polygraphy, $tcCO_2$ and CBG, daytime and morning.

Data collection

After inclusion, all patients will be assessed with the Edinburgh Cognitive and Behavioral ALS Screen (ECAS [8]) the Epworth Sleepiness Scale (ESS [9]), the Pittsburgh Sleep Quality Index (PSQI [10]) and spirometry (Vitalograph Spirotrac). Data collected will be used for demographic descriptions, and other relevant demographic variables will also be collected.

All data except the ECAS are collected directly in REDCap, a secure web platform for online databases and surveys. The ECAS is performed on paper by an ECAS-certified person.

At the three-month follow-up, patients are asked to rate their satisfaction with the NIV and the process of initiating NIV (PREMs) on a 1-5 numerical rating scale (NRS), where one indicates less satisfaction, and five indicates the highest satisfaction. The ESS and the PSQI are measured again.

Outcome measures

The primary outcome is median daily use (in minutes) of NIV during the seven days preceding the three-month follow-up, at which time treatment is expected to be stable.

Secondary outcomes

This study has two main secondary outcomes: patient satisfaction with NIV (NRS 1-5) at the three-month follow-up, and patient satisfaction with the process of initiating NIV (NRS 1-5) at the three-month follow-up.

For further exploratory outcomes, please see Supplement 2.

Adverse events and reactions

At the three-month follow-up, all patients are asked about adverse events using a binary questionnaire (yes/no)

concerning adverse effects and reactions to the NIV treatment.

Statistics

p values < 0.05 will be considered statistically significant. Normally distributed data will be presented as mean and standard deviation, and differences between groups will be analysed using the unpaired t-test. Non-normally distributed data will be presented as median and percentiles, and group differences will be tested using the Mann-Whitney U test. Categorical variables will be compared using the chi-squared test or Fisher's exact test, as appropriate.

Sample size

We defined a clinically relevant difference of 60 minutes for the primary endpoint (NIV use) between the outpatient and inpatient groups, as differences of less than 60 minutes were deemed clinically irrelevant. Based on the results of a previous study [11], we calculated that a sample size of 46 patients (23 in each group) would enable us to detect a non-inferior difference of 60 minutes with a power of 80% and a type I error risk of 5%, accounting for a 10% drop-out.

Major protocol violation

All randomised patients who start treatment will be included in the intention-to-treat analysis.

Patients who start treatment but die during the three-month study period will be included in the intention-to-treat analysis, with primary outcome measured in the last seven days before death. These patients will be excluded from the per-protocol analysis because compliance cannot be measured at three months after initiating NIV.

Patients who start treatment but withdraw from the study within three months of follow-up will be included in the intention-to-treat primary analysis using data from the seven days leading up to the date of withdrawal but will be excluded from the per-protocol analysis.

If a patient is not ready to be discharged after NIV initiation according to the protocol (e.g. patients in the outpatient group who will need to stay in-hospital for at least one night), this will be registered as a major protocol violation. Such patients will be excluded from the per-protocol analysis but included in the intention-to-treat analysis.

Finally, patients without accessible data at the three-month follow-up who report using the treatment will be included in the intention-to-treat analysis. They will be assigned an NIV use time of 25% of the lowest value in their group. They will be excluded from the per-protocol analysis.

Ethics and dissemination

The study will be conducted in accordance with this study protocol and with the Helsinki Declaration. It has been approved by the Research Ethics Committee of Copenhagen (H-23005093) and registered in the hospital's electronic research system (Privacy). Additionally, it has been registered with ClinicalTrials.gov (NCT05829330).

All participating patients will provide written informed consent before initiating NIV. This consent will be uploaded to the patients' medical records. Participants will have the opportunity to request information about the study results, which can be shared once data analysis is completed.

The study's findings will be presented at relevant scientific conferences, and the trial results will be submitted for publication in a peer-reviewed journal.

Data sharing statement

De-identified data and supporting documents will be available from the principal investigator upon reasonable request, subject to proposal review and a data access agreement, for up to five years after publication.

Trial registration: NCT05829330.

DISCUSSION

This randomised, controlled study will compare outpatient NIV initiation with telemonitoring to standard care in patients with ALS, focusing on adherence to treatment and patient-related outcomes. The outpatient approach may reduce waiting time and hospital admissions while reducing healthcare costs [11]. Furthermore, telemedicine follow-up may improve patient satisfaction by reducing the need for hospital visits.

Previous studies investigating outpatient initiation of NIV compared with inpatient have found that outpatient NIV is non-inferior to standard treatment regarding adherence and time needed to adapt to treatment. However, these studies have either included only patients with COPD [11], a wide variety of patients with restrictive thoracic conditions, been retrospective studies [12], compared with standard care of 5-7 days hospitalisation, or assessed the effect of a complex and resource-intensive setup with initiation at home by a specialised nurse [11].

One of the main strengths of the present study is that all included patients are within the same diagnostic group, i.e. patients with a severe, progressive and life-limiting condition. This increases internal validity as patients share comparable disease trajectories and prognoses. Another important strength is the computer-based randomisation with stratification for bulbar involvement, as this condition is associated with reduced NIV compliance [13, 14]. Moreover, it is a single-centre study in which all patients are initiated by only two doctors. The primary outcome is assessed by another blinded doctor.

Adherence to treatment is selected as the primary outcome, serving as a surrogate marker for optimal ventilation, since the therapeutic effect of ventilation depends on consistent and sustained use. At study termination, the effect of ventilation will be assessed in all participants through a nocturnal polygraphy combined with CBG. As a secondary outcome, we focus on PREMs and patient involvement by asking about treatment satisfaction and care pathway satisfaction. Also, patients are asked about their preferred initiation group prior to randomisation to determine if this is a potential study limitation.

There is a risk of selection bias if patients decline participation specifically because they do not wish to initiate treatment as outpatients, leaving only patients with a positive attitude towards outpatient care. However, all eligible patients are screened, and the reasons for exclusion are described.

Moreover, patients with ALS may struggle to accept a nasal mask due to, e.g. facial muscle weakness, and will require a full-face mask covering both nose and mouth. In Denmark, patients requiring full-face masks with insufficient hand function are assigned a team of respiratory caregivers to observe treatment and ensure mask removal in the event of vomiting. These patients follow a different treatment trajectory. However, excluding these participants could introduce selection bias and reduce the generalisability of the study findings. Neuropsychological impairment may affect adherence to mask treatment, and all patients were evaluated by an investigator using the ECAS. The investigator had completed formal ECAS training prior to administering the test. However, we used a Danish version of the ECAS that has not yet undergone formal validation, which represents a methodological limitation.

The findings of this study may change the care pathway for NIV initiation in patients with ALS. Moreover, the results may be applicable to other patient populations, such as those with obesity hypoventilation syndrome. External validity is presumed to be high, as patients with ALS may be among the most challenging groups to initiate NIV treatment.

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