HOME TELEMONITORING OF NON INVASIVE VENTILATION DECREASES HEALTHCARE UTILIZATION IN A PROSPECTIVE CONTROLLED TRIAL OF ALS PATIENTS

Anabela Pinto^{1,2}, MD, PhD; José Pedro Almeida^{1,2}, MD; Susana Pinto², MD; João Pereira
BsC;³ António Gouveia Oliveira⁴, MD, PhD; Mamede de Carvalho^{2,5}, MD, PhD.

¹Department of Physical Medicine and Rehabilitation, Santa Maria Hospital, Lisbon, Portugal

²Neuromuscular Unit, Instituto de Medicina Molecular, Faculty of Medicine, Lisbon, Portugal

³ Linde Homecare Co, Lisbon, Portugal

⁴Department of Biostatistics, Faculty of Medical Sciences, Universidade Nova de Lisboa,
Portugal

⁵ Department of Neurosciences, Santa Maria Hospital, Lisbon, Portugal

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Address for correspondence:

Anabela Pinto, MD, PhD

Clínica Universitária de Medicina Física e de Reabilitação

Hospital de Santa Maria

Av. Prof. Egas Moniz, 1649-028 Lisboa

Portugal

Phone: 00 351 917 600 305

Fax: 00351217805577

E-mail (can be published): jsanches.apinto@mail.telepac.pt;

anabela.pinto@hsm.min-saude.pt

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Abbreviations:

ALS	Amyotrophic Lateral Sclerosis
ALSFRS	Amyotrophic Lateral Sclerosis Functional Rate Scale
Back-up rate	Imposed breath frequency
DTC	The number of days needed to achieve full compliance (NIV use $\geq$ 6 hours a day)
EPAP	Expiratory Positive Air pressure
ES	Expiratory sensitivity
FVC	Forced Vital Capacity
MIP	Maximal Inspiratory Pressure
I:E	Inspiratory/ expiratory ratio
IPAP	Inspiratory Positive Air pressure
IS	Inspiratory sensitivity
NIV	Non-Invasive Ventilation
RFT	Respiratory Function Tests
rT	Rise time

ABSTRACT

Background. Non-Invasive Ventilation (NIV) is an efficient method for treating respiratory failure in ALS patients. However, it requires a process of adaptation not always achieved due to poor compliance. The role of telemonitoring of NIV is not yet established. **Objectives:** to test the advantage of using modem communication in NIV of ALS patients. **Design:** prospective, single-blinded controlled trial. **Population and methods:** According to their residence, 40 consecutive ventilated ALS patients were assigned: to a control group (G1, n=20) in which compliance and ventilator parameter settings were assessed during office visits; or to an intervention group (G2, n=20) in which patients received a modem device connected to the ventilator. The number of office and emergency room visits and hospital admissions during the entire span of NIV use and the number of parameter setting changes to achieve full compliance were the primary outcome measurements. **Results:** Demographic and clinical features were similar between both groups at admission. No difference on compliance was found between groups. The incidence density of changes in parameter settings throughout the survival period with NIV was lower in G2 ($p<0.0001$), but it was increased during the initial period needed to achieve full compliance. The incidence density of the number of office or emergency room visits and in-hospital admissions was significantly lower in G2 ($p<0.0001$). Survival showed a trend favoring G2 ($p=0.13$). **Conclusions.** This study shows that telemonitoring reduces health care utilization with probable favorable implications on costs, survival and functional status.

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a progressive and fatal neurodegenerative disease in which respiratory insufficiency is the most common terminal event. Non-invasive positive pressure ventilation (NIV) has become the standard management to respiratory impairment by increasing quality of life and reducing the likelihood of resorting to tracheostomy [1-9]. Improved rate of survival and quality of life seem to correlate with the earlier prescription of NIV, before diurnal signs of respiratory failure have been established, with a forced vital capacity (FVC) over 50% of the predicted value, or at detection of early signs of impending nocturnal respiratory insufficiency [8, 10-12].

NIV requires a dynamic process of adaptation which is achieved in an unknown proportion of patients. Probably, patients with severe bulbar weakness and marked sialorrhea have the highest rate of poor compliance [13, 14]. In fact, compliance to NIV is a complex issue and a recent matter of debate [10, 15-18]. Certainly, improved tolerance and compliance can only be reached by continuous, customized setting of the device that depends on many factors, such as lung mechanics [17, 19], inspiratory and expiratory triggers, breathing frequency [20-22], effective correction of blood gases [13, 23], and different metabolic demands. The compliance to NIV in ALS has only been evaluated taking into account the number of hours of usage a day, which is very limited information. Nevertheless, most authors have reported longer survival in patients using NIV for more than 4 hours per day [3, 23-25].

Recent technology advances allow a more extensive control of the relevant sets in addition to the analysis of the number of hours/day of utilization. It is possible to assess breath pressures and volumes, the percentage of utilization of a predetermined target pressure, respiratory rate, peak flow, number of apneas, percentage of leaks, and oxygen saturation on pulse oximetry. It is also possible to perform online checking and correction via modem connection, hopefully increasing patient comfort, tolerance and compliance [26]. Nonetheless, the advantages of these new technologies have scarcely been evaluated in neuromuscular patients [27].

To the best of our knowledge, only one study has compared the effectiveness of an outpatient initiation protocol with the standard in-hospital model for NIV [23]. No study has yet evaluated the impact on compliance, function, survival and healthcare utilization of ALS patients submitted to wireless telemetry to control NIV settings, compared with the office-visit approach. We aimed to investigate this relevant problem

PATIENTS AND METHODS:

From January 2003 to September 2006, all consecutive ALS patients ventilated with Goodknight 425ST® bi-level device (Tyco Healthcare Group LP, CA) were screened and considered for inclusion in a prospective and controlled trial, if at diagnosis they had no signs or symptoms of respiratory insufficiency with $FVC \geq 75\%$ of the predicted value, $PaO_2 \geq 80\text{mmHg}$ and $PCO_2 \leq 45\text{mmHg}$ and age between 18-75 years. Patients with gastrostomy, cognitive impairment, or other significant disorders, were also excluded from this trial. Patients were randomly assigned to one of two groups according to their residential area. Patients included in G1 (control) were living in Lisbon, in this group the managing of NIV settings and assessment of compliance was performed through regular office visits at admission, 2-3 weeks later, and then every 3 months. Patients included in G2 (intervention) were living outside Lisbon and the follow-up was performed by weekly modem-tele monitoring, in addition to regular office-visits at each three-month interval. All participants were evaluated with the ALSFRS each 3 months by a physician blind to the study group of the patient. Respiratory functional tests (RFT) were performed each 6 months by a technician unaware of this study. All received a helpline whenever needed, in addition to regular office visits [28,29]. The trial duration was established from NIV adaptation to a follow period of 3 years or death.

ALS patients were ventilated taking into account a set of criteria that included clinical symptoms, conventional respiratory function tests as recommended by AAN [2] (including FVC and maximal inspiratory pressure), neurophysiologic studies and nocturnal pulse oximetry [10, 11]. NIV was indicated as early as patients agreed after the first symptoms and signs of changes, in an office-based setting. NIV is optimized to improve clinical symptoms and nocturnal pulse oxymetric changes. The procedure include slow increments of Inspiratory Positive Air pressure (IPAP) in order to achieve a steady-state with normal breathing patterns, normal pulse rate and SpO_2 over 95%, with the back-up rate slightly lower than the patient's own respiratory frequency.

For NIV compliance follow-up and flexible parameter settings changes, all participants received a helpline to clarify any doubts or to seek medical advice whenever difficulties were felt. Patients in G1 were, in addition, re-observed 2-3 weeks after entry, and patients in G2 had a modem pre-installation programmed to communicate every week. Anticipating difficulties and constraints imposed by continuously monitoring and data storing, patients in G2 were further instructed to activate the system once a week or whenever they felt uncomfortable with the device, after giving a phone call to the physician in charge, and instructed to be in touch with the helpline in case of need.

A crucial element of the telemedicine instrument functionality is the remote transmission of data. The instrument is equipped with an internal modem, allowing direct access to the Internet via TCP/IP protocol along with data storing at the patient's home. The bi-directionality of the system allowed us not only to register compliance data but also to introduce modifications in parameter settings, thus permitting real-time evaluation of its impact on ventilatory mechanics. Regarding the device used in this study the bi-level instrument included backup rate/assist control as well as patented FlowSens technology that allow the physician to customize the inspiratory and expiratory settings for greater patient comfort and synchronicity.

In addition, an intermediate level of care was set up to detect and flag alarm signs requiring an immediate revision of settings. This monitoring was performed by one of us (JP) who, after reviewing the synthesis report or night calendar, was instructed to send a message to the physician who decided on possible setting change, to schedule an office visit, a phone call or a real-time communication. Since, there are no published or established alert signs for home ventilation, in rapidly progressive neuromuscular disorders, we considered all data that were $\pm 1SD$ of the mean values of IPAP, expiratory positive air pressure (EPAP), Inspiratory/expiratory ratio (I: E), back-up rate, inspiratory sensitivity (IS), expiratory sensitivity (ES) and rise time (rT), as alert signs. These limits were defined by data analysis of 67 ALS with regular NIV use ≥ 6 hours a day followed in our Unit (unpublished data). In addition, we

also considered as an alert sign all data conflicting with the preceding ventilation profile of the patient.

Primary Outcome

We considered 2 primary outcomes measurements. First, the number of office and emergency room visits, and hospital admissions during the entire span of NIV use; second, the number of parameter setting changes during the period (number of days, DTC) needed to achieve full compliance (defined as NIV use >6 hours) and throughout all period of NIV use.

Secondary Outcomes

As secondary outcome measures we considered the clinical and functional disease progression as defined by ALSFRS total score, respiratory, spinal and bulbar sub-score (every 3 months), RFT (very six months), the total survival (total number of days from symptoms onset to death or the end of the study), survival from first visit (total number of days from diagnosis to death or end of study) and survival with NIV (total number of days from NIV adaptation to death or end of the study). In addition, we also recorded the type of parameter setting change and the compliance, assessed by the number of hours of usage a day; the percentage of spontaneous breathing; back-up respiratory rate; average, minimum and maximal respiratory rates; and the percentage of attained predetermined pressures.

In this study, all patients gave written informed consent, after protocol approval by the local Ethics Committee and since this is a pilot study, sample size considerations were not based on a predefined clinical significant difference in health resource utilization and survival probability, but rather on studying the minimal number of subjects (20 per group) that would allow the application of large sample statistical methods.

Statistical Analysis

Demographic and baseline clinical and respiratory function data were analysed for homogeneity between groups with two-sample t-tests and Fisher's exact test. Event count data, such as health care utilization data (number of office visits, hospital admissions and emergency room admissions, the number of parameters changes and number of DTC were

analysed with the person-years method and reported as incidence rate ratios with exact Poisson confidence intervals and significance tests. Repeated measurements data (panel data) on parameters settings and patient compliance were analyzed with random effects regression. Survival was analysed with the Kaplan-Meier method and survivor functions were compared with the log rank test. Student's t-tests and the Fisher's exact test were used throughout as appropriate. Differences were considered statistically significant at the $p < 0.05$ level. All tests are two-tailed. Statistical analysis was performed with STATA 10 (Stata Corporation, College Station, TX, USA).

RESULTS:

Out of 155 consecutive home-ventilated ALS patients, 51 were excluded because they were ventilated with devices that did not allow compliance analysis through modem communication. A group of 62 additional patients were excluded because had FVC lower than 75% of the predicted value. Among the 42 eligible patients, two patients refused to participate and were excluded. The final analysis set consisted of 20 patients in the control group (G1) and 20 patients in the intervention group (G2), but one patient in G2 was lost for follow-up and excluded from analysis. (Figure 1) No difference was found regarding demographic data, clinical characteristics and respiratory function tests between groups both at diagnosis and at NIV adaptation, except for FVC that was significantly higher in G1 at diagnosis ($p=0.04$) - Tables 1 and 2. Moreover, mean values of the initial parameter settings of NIV at the time of non-invasive ventilation onset were not different, showing that the procedure was the similar in both groups.

Primary outcome

Table 3 shows incidence data regarding the number of office and emergency room visits and in-hospital admissions. The incidence rate was three to six times lower in G2 patients ($p < 0.0001$). Random-effects regression analysis of the overall difference in the type of parameter settings changes throughout the ventilation period showed no differences between groups. The same negative results were observed in the comparison of compliance data, although a trend towards a greater number of daily hours of NIV use in Group 2 was observed ($p = 0.17$).

Secondary outcomes

The incidence rate of the number of changes in parameter settings during DTC and over the entire period of NIV showed a slightly higher incidence rate in G2 during the initial period of adaption (20%, $p < 0.01\%$) but a clearly lower rate over the entire period of NIV (50%, $p < 0.0001$) – table 4.

The clinical progression rate prior to NIV adaption showed no differences between groups for the total ALSFRS score, as well as for bulbar and spinal subscores. Respiratory subscore tended to progress faster in G1 ($p=0.04$). However, after NIV adaptation, the random-effects general linear model regression analysis did not show statistically significant differences in the clinical progression, despite of a trend for slower progression of spinal subscore in G2 ($p=0.15$).

Considering survival evaluation, at study finish 12 patients were still alive in each group and differences did not reach statistical significance at the 5% level. However, patients included in G2 tended to have a longer survival (table 5 and figure 2).

DISCUSSION:

ALS is a dreadful neurological condition with a low incidence of 2-4/100.000 inhabitants, short survival and low prevalence of 5-7/100000 according to different epidemiological studies[30]. The relatively small number of patients supports some difficulties in the randomization of patients based on computer generation in a single centre in our country. Thus, the present study is a prospective single-blinded quasi-randomized clinical trial that included consecutive patients, aimed to test the feasibility, efficacy and efficiency of telemedicine for home monitoring NIV. In addition, the patient selection based on geographical residence was not considered biased and, probably, appropriated to our purpose.

The feasibility of telemedicine for home monitoring patients with chronic respiratory failure (CRF) discharged from hospital in COPD patients within a mean follow-up time of 176 days has been assessed and showed that home monitoring was feasible, and useful for titration of ventilation settings[31].

To the best of our knowledge the present study is the first trial of NIV compliance evaluation with the new technical solution that enabled us to monitor at distance the registered data in the equipment software.

Before the present trial, in the run-in period, we had an exploratory phase to test safety, acceptance and accuracy. The system was suitable worked well and served our investigational purposes. Main limitations were related to the need of a fixed telephone line and the speed of data extraction.

Our study supports the role and utility of tele-monitoring in eliminating difficulties imposed by geographical distances and the lack of resources. We observed objective gains in terms of health care utilization (table 3) reflecting the efficiency of the system.

Cost analysis is underway, but our preliminary data indicates significant cost reduction using telemonitoring (approximately 50%), as expected from the lower number of hospital visits and admissions. Therefore, in view of the limited resources of health systems[32, 33], this study strongly supports that the frequent virtual visits to the patients by modem

communications may become current practice, as an alternative to the office-based control of compliance to NIV.

Indeed the control of compliance is a critical issue because, despite recommendations, the rate of NIV use is poor and highly variable (range 0-70%) in European and American ALS centers. Chiò and co-workers showed that the use of NIV ranged from 50-70% depending on the size of the ALS clinics. More recently, Jackson reported 36% use in ALS patients with FVC lower than 50% of the predicted value, and correlated tolerance to respiratory symptoms. Other factors like age, race, type of insurance, forced vital capacity, disease duration, ALSFRS, caregiver burden or quality of life were not predictors of compliance [18, 34-37].

Other reasons may implicate the possible relationship of compliance to settings of the ventilators. The possible role of setting changes through modem communications in increasing compliance was not confirmed in the present study, probably due to the identical procedures that took place in both groups, all performed by one of the authors (AP) or due to the small sample size. However, our results showed a trend towards a greater number of hours of NIV use in G2, suggesting a marginal effect on compliance. Probably associated with this marginal effect, we observed a trend toward a survival benefit ($p=0.17$) in G2, table 5.

In addition, in G2 we were able to show 50% reduction in the number of parameter setting changes during the survival period with NIV, but 20% increase during the DTC period (exact Poisson $p<0.001$). This result represents a tighter follow-up during the initial period of NIV adaptation, thus driving a reduction of the total time need to adjust settings over the whole period of ventilation.

Regarding the functional and survival outcome measures, the median survival with NIV was 334 days in G1 versus 865 days in G2 ($p=0.13$). Considering the survival from symptoms onset, the benefit in the median survival time was over 1500 days (figure 2). Further calculations of the sample needed to achieve 90% of statistical power resulted in a number of 40 patients in each arm to show a significant survival impact.

Moreover, a trend was also observed toward an improved functional outcomes in G2 patients, regarding ALSFRS spinal sub score ($p = 0.15$). This was not anticipated, as ALS patients in G1 had a closer follow-up provided by physiotherapy in our specialized centre. Exercise was suggested to all patients included to the limits of perceived fatigue (Borg scale), simultaneously with NIV if needed [15], but patients in G1 were supervised by physiotherapists with special training in ALS. We hypothesise that timed and adequate intervention due to early detection of alert signs might allow patients to perform more daily physical activities. Ventilation subtleties may be not fully understood without quantifying measurements related to lung mechanics, meaning that clinical judgment may not be sensitive enough to early detect deviations from a ventilation profile otherwise detected by the regular observation of the night calendar. The increased speed of these communications with faster data transmission and improved alarm signs would certainly reassure patients, caregivers and physicians with benefits to all [38].

Whether our positive results are related to closer vigilance and faster correction of respiratory changes or to other undisclosed factor remains to be clarified. Future studies should evaluate impact of telemonitoring on the quality of life of patients and caregivers.

Figure 1: Population and methods (flow chart)

Table 1: Demographic and baseline clinical characteristics at diagnosis

	Group 1 (n=20)		Group 2 (n=19)		
	<i>mean</i>	<i>sd</i>	<i>mean</i>	<i>sd</i>	<i>p-value</i>
Age (years)	60	10	62	12.90	0.66
Gender	14 M; 6F		13 M; 6 F		1.00
Type of onset	16 Sp; 4B		10 Sp; 9B		0.07
Disease duration (days)	308	156	362	296	0.44
ALSFRS (B sc)	11.0	2	10.0	2.00	0.65
ALSFRS (Sp sc)	22	4	23	4.40	0.48
ALSFRS-R (R)	10.7	2	12	2.30	0.46
ALSFRS (T)	33.0	4	33.0	4.30	0.63
FVC (%)	101.87	17.66	90.52	13.49	0.04
MIP (%)	55.88	25.06	55.22	23.29	0.94
MEP (%)	71.19	20.30	72.43	23.48	0.88
P0.1 (%)	69.78	43.87	97.25	33.75	0.07
PaCO2 mmHg	38.67	4.44	40.80	14.37	0.59
PaO2 mmHg	85.56	8.75	83.53	15.25	0.65

ALS-FRS – ALS functional rating scale (B sc - bulbar subscore, Sp sc – spinal subscore,

ALSFRS-R (R) – respiratory subscore of ALS-FRS-R); FVC (forced vital capacity), MIP

(maximal inspiratory pressure), MEP (maximal expiratory pressure) and P01 (mouth

occlusion pressure at 100ms) are expressed in percentage of the predicted value; sd – standard deviation.

Table 2: Respiratory evaluation at NIV adaptation

	Group 1	Group 2	
	(m $\pm$ sd); range (min-max)	(m $\pm$ sd); range (min-max)	p-value
FVC (%)	(76 $\pm$ 23);(55-122)	(85 $\pm$ 20);(54-119)	0.32
MIP (%)	(42 $\pm$ 28);(10-89)	(50 $\pm$ 20);(13-89)	0.40
MEP (%)	(44 $\pm$ 24);(13-98)	(54 $\pm$ 21);(15-86)	0.24
P0.1 (%)	(101 $\pm$ 39);(51-196)	(91 $\pm$ 54);(39-231)	0.61
PaCO2 (mmHg)	(42 $\pm$ 7);(35-59)	(40 $\pm$ 5);(35-52)	0.46
PaO2 (mmHg)	(83 $\pm$ 15);(55-106)	(84 $\pm$ 8);(71-95)	0.88

See abbreviations in table 1 footnote.

Table 3: Results of Primary Outcome, health care utilization

	Incidence density (% person-days)		Incidence rate ratio	95% C. I	p-value
	Group 1	Group 2			
Office visits	9.01	3.02	0.336	0.293-0.384	<0.0001
Emergency room	0.58	0.11	0.194	0.099-0.373	<0.0001
visits					
Hospital admissions	0.37	0.06	0.173	0.066-0.407	<0.001

It is represented the confidence intervals (CI) and p values by applying exact Poisson statistics.

Table 4: Secondary outcome, incidence rate of parameters settings number of changes

	Incidence density (% person-days)		Incidence rate ratio	95% CI	p-value
	Group 1	Group 2			
Changes/ NIV	1.70	0.91	0.533	0.401-0.711	<0.0001
Changes/DTC	7.69	9.52	1.238	0.930-1.651	<0.001

Incidence density is the person-time incidence rate. Incidence rate ratio is the ratio of the incidence density G1/G2. Changes/ NIV relates to the total period of NIV; Changes/DTC concerns the period from NIV onset to full compliance (>6 hours/day).

It is represented the confidence intervals (CI) and p values by applying exact Poisson statistics.

Table 5: Survival analysis.

	Group 1 (n=20)	Group 2 (n=19)	
	Median (days)	Median (days)	p-value
Survival with NIV	334	865	0.13
Survival from onset	1457	>3108	0.14
Survival from 1st visit	1092	1645	0.13

Legend:

Survival with NIV is the number of days from NIV adaptation to death; Survival from onset is the number of days from symptoms onset to death; Survival from first visit is the number of days from diagnosis to death.

Figure 2: Kaplan-Meier survival curves

Legend: Group 1 included 20 patients whose compliance to NIV was office based. Group 2 included 19 patients to whom a remote control of their equipments was offered. At the end of the study 12 patients were alive in each group.

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Author's role:

Anabela C Pinto: responsible for study design, follow-up of patients (respiratory care and equipments) and supervised data collection, analysis and manuscript preparation

José Pedro Almeida gave a substantial collaboration in data collection, analysis and in the preparation of the manuscript

João Pereira was responsible for the intermediate level of respiratory care, as well as detecting and flag the alarm signs previously accorded.

Susana Pinto gave her collaboration in the follow-up of patients (neurological care) as well as in manuscript preparation

António O. Gouveia was responsible for the statistical procedures, analysis, review and also gave an important collaboration in the manuscript preparation

Mamede de Carvalho gave his collaboration to obtain local ethics committee approval, patients informed consent, advise and help in all project phases including manuscript preparation, and responsible for the follow-up of patients (neurological care)

Competing interests

The authors disclose any personal or financial support or involvement with organizations with financial interest with the subject matter or any actual or potential conflict of interests

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Anabela Pinto

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Lisboa, 15th December 2009

Mamede de Carvalho

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Susana Pinto

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José Pedro Almeida

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António Oliveira Gouveia

REFERENCES

1. Annane, D., et al., *Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders*. Cochrane Database Syst Rev, 2007(4): p. CD001941.
2. Miller, R.G., *Examining the evidence about treatment in ALS/MND*. Amyotroph Lateral Scler Other Motor Neuron Disord, 2001. **2**(1): p. 3-7.
3. Pinto, A.C., et al., *Respiratory assistance with a non-invasive ventilator (Bipap) in MND/ALS patients: survival rates in a controlled trial*. J Neurol Sci, 1995. **129 Suppl**: p. 19-26.
4. Lyall, R.A., et al., *A prospective study of quality of life in ALS patients treated with noninvasive ventilation*. Neurology, 2001. **57**(1): p. 153-6.
5. Heffernan, C., et al., *Management of respiration in MND/ALS patients: an evidence based review*. Amyotroph Lateral Scler, 2006. **7**(1): p. 5-15.
6. Annane, D., et al., *Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders*. Cochrane Database Syst Rev, 2007(4): p. CD001941.
7. Servera, E. and J. Sancho, *Appropriate management of respiratory problems is of utmost importance in the treatment of patients with amyotrophic lateral sclerosis*. Chest, 2005. **127**(6): p. 1879-82.
8. Lechtzin, N., et al., *Early use of non-invasive ventilation prolongs survival in subjects with ALS*. Amyotroph Lateral Scler, 2007. **8**(3): p. 185-8.
9. Hogle, D.H., *Should your hospital implement wireless solutions?* Biomed Instrum Technol, 2005. **Suppl**: p. 30-1, 33-4.
10. Pinto, A., et al., *Nocturnal pulse oximetry: a new approach to establish the appropriate time for non-invasive ventilation in ALS patients*. Amyotroph Lateral Scler Other Motor Neuron Disord, 2003. **4**(1): p. 31-5.
11. Jackson, C.E., et al., *A preliminary evaluation of a prospective study of pulmonary function studies and symptoms of hypoventilation in ALS/MND patients*. J Neurol Sci, 2001. **191**(1-2): p. 75-8.
12. Lechtzin, N., *Respiratory effects of amyotrophic lateral sclerosis: problems and solutions*. Respir Care, 2006. **51**(8): p. 871-81; discussion 881-4.
13. Bach, J.R., *Amyotrophic lateral sclerosis: prolongation of life by noninvasive respiratory AID*. Chest, 2002. **122**(1): p. 92-8.
14. Bach, J.R., C. Bianchi, and E. Aufiero, *Oximetry and indications for tracheotomy for amyotrophic lateral sclerosis*. Chest, 2004. **126**(5): p. 1502-7.
15. Pinto, A.C., et al., *Can amyotrophic lateral sclerosis patients with respiratory insufficiency exercise?* J Neurol Sci, 1999. **169**(1-2): p. 69-75.
16. Pinto, A.C., et al., *Respiratory disorders in ALS: sleep and exercise studies*. J Neurol Sci, 1999. **169**(1-2): p. 61-8.
17. Wyatt, J. and F. Bellis, *British Thoracic Society guidelines on non-invasive ventilation*. Emerg Med J, 2002. **19**(5): p. 435.
18. Jackson, C.E., et al., *Factors correlated with NPPV use in ALS*. Amyotroph Lateral Scler, 2006. **7**(2): p. 80-5.
19. Babu, K.S. and A.J. Chauhan, *Non-invasive ventilation in chronic obstructive pulmonary disease*. Bmj, 2003. **326**(7382): p. 177-8.

20. Baydur, A., et al., *Long term non-invasive ventilation in the community for patients with musculoskeletal disorders: 46 year experience and review.* Thorax, 2000. **55**(1): p. 4-11.
21. Aghai, Z.H., et al., *Synchronized nasal intermittent positive pressure ventilation (SNIPPV) decreases work of breathing (WOB) in premature infants with respiratory distress syndrome (RDS) compared to nasal continuous positive airway pressure (NCPAP).* Pediatr Pulmonol, 2006. **41**(9): p. 875-81.
22. Achour, L., et al., *Asynchrony and cyclic variability in pressure support noninvasive ventilation.* Comput Biol Med, 2007. **37**(9): p. 1308-1320.
23. Lujan, M., et al., *Non-invasive home mechanical ventilation: effectiveness and efficiency of an outpatient initiation protocol compared with the standard in-hospital model.* Respir Med, 2007. **101**(6): p. 1177-82.
24. Aboussouan, L.S., et al., *Objective measures of the efficacy of noninvasive positive-pressure ventilation in amyotrophic lateral sclerosis.* Muscle Nerve, 2001. **24**(3): p. 403-9.
25. Farrero, E., et al., *Outcome of non-invasive domiciliary ventilation in elderly patients.* Respir Med, 2007. **101**(6): p. 1068-73.
26. Fiorenza, D., M. Vitacca, and E. Clini, *Hospital monitoring, setting and training for home non invasive ventilation.* Monaldi Arch Chest Dis, 2003. **59**(2): p. 119-22.
27. Lucangelo, U., F. Bernabe, and L. Blanch, *Lung mechanics at the bedside: make it simple.* Curr Opin Crit Care, 2007. **13**(1): p. 64-72.
28. *The Amyotrophic Lateral Sclerosis Functional Rating Scale. Assessment of activities of daily living in patients with amyotrophic lateral sclerosis. The ALS CNTF treatment study (ACTS) phase I-II Study Group.* Arch Neurol, 1996. **53**(2): p. 141-7.
29. Mendoza, M., et al., *A comparison of maximal inspiratory pressure and forced vital capacity as potential criteria for initiating non-invasive ventilation in amyotrophic lateral sclerosis.* Amyotroph Lateral Scler, 2007. **8**(2): p. 106-11.
30. Wijesekera, L.C. and P.N. Leigh, *Amyotrophic lateral sclerosis.* Orphanet J Rare Dis, 2009. **4**: p. 3.
31. Vitacca, M., et al., *A pilot study of nurse-led, home monitoring for patients with chronic respiratory failure and with mechanical ventilation assistance.* J Telemed Telecare, 2006. **12**(7): p. 337-42.
32. de Lusignan, S., et al., *A pilot study of radiotelemetry for continuous cardiopulmonary monitoring of patients at home.* J Telemed Telecare, 2000. **6 Suppl 1**: p. S119-22.
33. Pfeifer, M., B. Werner, and H. Magnussen, *[Telecare of patients with chronic obstructive airway diseases].* Med Klin (Munich), 2004. **99**(2): p. 106-10.
34. Bourke, S.C., et al., *Noninvasive ventilation in ALS: indications and effect on quality of life.* Neurology, 2003. **61**(2): p. 171-7.
35. Bradley, W.G., et al., *Changes in the management of ALS since the publication of the AAN ALS practice parameter 1999.* Amyotroph Lateral Scler Other Motor Neuron Disord, 2004. **5**(4): p. 240-4.
36. Miller, R.G., et al., *Outcomes research in amyotrophic lateral sclerosis: lessons learned from the amyotrophic lateral sclerosis clinical assessment, research, and education database.* Ann Neurol, 2009. **65 Suppl 1**: p. S24-8.

37. Chio, A. and V. Silani, *Amyotrophic lateral sclerosis care in Italy: a nationwide study in neurological centers*. J Neurol Sci, 2001. **191**(1-2): p. 145-50.
38. Tura, A., et al., *A telemedicine instrument for home monitoring of patients with chronic respiratory diseases*. Ann Ist Super Sanita, 2007. **43**(1): p. 101-9.

Figure 1: Population and methods (flow chart)

Figure 2: Kaplan-Meier survival estimate curves

Legend: Group 1 included 20 patients whose compliance to NIV was office based. Group 2 included 19 patients to whom a remote control of their equipments was offered. At the end of the study 12 patients were alive in each group.