BMJ Open

Effects of respiratory physiotherapy in patients with amyotrophic lateral sclerosis: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061624
Article Type:	Protocol
Date Submitted by the Author:	01-Feb-2022
Complete List of Authors:	Pondofe, Karen; Universidade Federal do Rio Grande do Norte Centro de Ciências da Saúde, aboratório de Inovação Tecnológica em Reabilitação e PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH) Marcelino, Ana; Universidade Federal do Rio Grande do Norte, aboratório de Inovação Tecnológica em Reabilitação e PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH) Ribeiro, Tatiana Souza; Federal University of Rio Grande do Norte, Departamento de Fisioterapia e Laboratório de Inovação Tecnológica em Saúde (LAIS), Hospital Universitário Onofre Lopes (HUOL), Empresa Brasileira de Serviços Hospitalares (EBSERH) Torres-Castro, Rodrigo; Universidad de Chile, Physiotherapy; Universidad de Chile Vera-Uribe, Roberto; University of Chile, Department of Physical Therapy Fregonezi, Guilherme; Universidade Federal do Rio Grande do Norte, Laboratório de Inovação Tecnológica em Reabilitação e PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH) Resqueti, Vanessa; Universidade Federal do Rio Grande do Norte, Fisioterapia, Laboratório de Inovação Tecnológica em Reabilitação e PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH)
Keywords:	Motor neurone disease < NEUROLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Neuromuscular disease < NEUROLOGY, REHABILITATION MEDICINE

Effects of respiratory physiotherapy in patients with amyotrophic lateral sclerosis: a systematic review protocol

Karen Pondofe[1,2,3]*, Ana Aline Marcelino[1,2,3], Tatiana Ribeiro[3,4], Rodrigo Torres-Castro[5,6], Roberto Vera-Uribe[5,6], Guilherme Fregonezi[1,2,6], Vanessa R Resqueti[1,2,6]

[1] Laboratório de Inovação Tecnológica em Reabilitação, Departamento de Fisioterapia, Universidade Federal do Rio Grande do Norte (UFRN), Natal, Campus Universitário Central, Natal, Rio Grande do Norte, Brazil.
[2] PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH), Universidade Federal do Rio Grande do Norte (UFRN), Natal, Rio Grande do Norte, Brazil.
[3] Departamento de Fisioterapia da Universidade Federal do Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil.
[4] Laboratório de Inovação Tecnológica em Saúde (LAIS), Hospital Universitário Onofre Lopes (HUOL), Empresa Brasileira de Serviços Hospitalares (EBSERH), Universidade Federal do Rio Grande do Norte (UFRN), Natal, Rio Grande do Norte, Brazil.
[5] Department of Physical Therapy, Faculty of Medicine, University of Chile, Santiago, Chile.
[6] International Physical Therapy Research Network (PhysioEvidence).

* Corresponding author: Karen Pondofe. Affiliations: Laboratório de Inovação Tecnológica em Reabilitação, Departamento de Fisioterapia, Universidade Federal do Rio Grande do Norte (UFRN). PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH), Universidade Federal do Rio Grande do Norte (UFRN), Natal, Rio Grande do Norte, Brazil.
Email address: karenpondofe@yahoo.com.br

Word Count: 1728

ABSTRACT

Introduction: Respiratory muscle weakness and ventilatory failure are common complications in patients with ALS and may lead to death. Respiratory physiotherapy may improve lung function in this population. This study aims to investigate the effects of respiratory physiotherapy on forced expiratory volume one second (FEV1), the forced vital capacity (FVC), peak cough flow, inspiratory reserve volume, and maximal respiratory pressures of patients with ALS. **Methods and analysis:** A protocol was published on PROSPERO (registration number CRD42021251842). The research will cover studies with no language or publication date restriction, available in the following databases: MEDLINE/PUBMED, EMBASE, Cochrane Library, Web of Science, and Physiotherapy Evidence Database. The research question will be answered using a search strategy adapted for each database. Searches in databases will be conducted from January 2021 to December 2022. Risk of bias will be assessed independently by two authors using the Cochrane risk-of-bias tool for randomized trials version 2. According to the results obtained, data will be reported as a meta-analysis or a narrative report. **Ethics and dissemination:** No previous ethical approval is required for this publication since data used is already published. Results of this review will be disclosed via peer-reviewed publications and conference presentations.

Keywords: Amyotrophic lateral sclerosis; forced vital capacity; inspiratory muscle weakness; functional capacity; respiratory insufficiency; nasal inspiratory pressure

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A comprehensive search for randomized controlled trial will be conducted in main databases.
- This systematic review will use the Cochrane Collaboration tool for assessing risk of bias.
- The difficulty in performing a randomized clinical trial may negatively interfere with quality of evidence.

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized by loss of cortical, brainstem, and spinal motor neurons. The average survival time from symptom onset is 3 to 5 years; however, survival may be longer in patients with slow disease progression [1].

Progressive respiratory muscle weakness is one of the main complications affecting patients with ALS [2]. Lung volume also reduces over time in these patients and leads to ineffective cough and worsening prognosis due to accumulation of secretions [3]. Respiratory failure is primarily determined by impaired inspiratory muscle strength associated with loss of motor unit of intercostal and axial muscles, a terminal event in ALS. Respiratory failure occurs mainly due to diaphragmatic weakness, associated with loss of motor unit of intercostal and axial muscles [4].

Forced vital capacity (FVC), maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP) are measures of respiratory function easily performed and monitored in the clinical environment. FVC is widely used in patients with ALS and associates with disease progression and survival (i.e., FVC of < 50% indicates the beginning of respiratory failure). Sniff nasal inspiratory pressure (SNIP) is considered a more accessible alternative than MIP for monitoring respiratory muscle strength [5]. It detects respiratory muscle strength, provides important prognostic information (SNIP of < 40 cmH_2O is associated with an average survival of 6 months), and accurately predicts nocturnal desaturation and respiratory failure in patients with ALS [6].

Decreased physical function negatively impacts activities of daily living during disease progression. The revised ALS Functional Rating Scale (ALSFRS-R) is strongly related to ALS survival and prognosis is used to assess and monitor the functional status of patients with ALS over time. It assesses speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed linen, walking, climbing stairs, and adds the breathing assessment sub-category [2, 7].

Respiratory system dysfunction is the terminal event for most patients with ALS [8, 9]. Respiratory muscle weakness reduce total lung capacity, vital capacity, and functional residual capacity and the measurements of respiratory muscle strength are essential for long-term monitoring of these patients [10]. Loss of phrenic nerve function causes diaphragm weakness, which may lead to further complication. Despite different presentations, most patients present impaired speaking and airway clearance due to reduced bulbar muscle coordination [11].

The combination of inspiratory muscle weakness and reduced chest wall compliance limits the amount of volume needed for an effective cough. Inspiratory capacity represents the volume inspired until the end of the inspiratory phase of cough and is considered the most determining factor for peak cough flow (i.e., affects length of expiratory muscle and efficiency of subsequent contraction). Also, adequate pressures to develop compressive forces and clear airway secretions are not achieved in the presence of glottic insufficiency. [12, 13, 14]

Impaired expiratory muscle contraction also decreases the ability to cough

and clear secretions. Physiotherapists should assess and monitor vital capacity, MIP, SNIP, or peak expiratory cough flow of patients with ALS at least every three months. [15, 16] physiotherapeutic interventions used in individuals with expiratory muscle weakness and secretion retention are lung volume recruitment, and airway clearance techniques with breath stacking, air stacking, and manually assisted coughing. [17, 18, 19, 20]

In addition, inspiratory muscle training, lung volume recruitment training, manually assisted coughing, and mechanical insufflation-exsufflation may also improve survival and should be included in the overall management of ALS. [16, 21]

This systematic review will investigate the effects of respiratory physiotherapy on forced expiratory volume one second (FEV1), the forced vital capacity (FVC), peak cough flow, inspiratory reserve volume, and maximal respiratory pressures of patients with ALS and monitor the variables symptom, ALSFRS-R, and rate of disease progression.

REVIEW QUESTION

“What are the effects of respiratory physiotherapy on lung function (capacities, volumes, and respiratory muscle strength), cough efficacy, and symptoms of patients with ALS?”

METHODS AND ANALYSIS

The study will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA-P) [22]. Searches in databases will be conducted from January 2021 to December

2022. The protocol for this review was submitted to the International Prospective Register of Systematic Reviews (CRD42021251842).

Eligibility criteria

Randomized controlled trial performed with adult patients, all ages, of both genders and diagnosed with definite, probable, probable laboratory-supported, possible, or suspected ALS will be included if full-text or sufficient information about respiratory therapy and results are present. Non-randomized studies found during the search will be considered for the discussion section. Main steps of the search phase will be reported using a PRISMA flow diagram (Figure 1). Studies performed with patients with neurodegenerative, cardiac, or respiratory diseases associated will be excluded.

[Insert figure 1]

Types of interventions

Intervention

Non-invasive respiratory physiotherapy techniques: breathing exercises, respiratory muscle training, air stacking, lung volume recruitment training, non-invasive ventilation, manually assisted cough, or mechanical insufflation-exsufflation.

Comparators

Placebo or any combination of other interventions designated as standard treatment or usual conventional care or no intervention will be considered for the control group.

Types of outcome measures

Primary outcomes

- Peak cough flow, used to assess cough efficiency by analyzing data from optoelectronic plethysmography;
- FVC and peak expiratory flow using spirometry;
- MIP and MEP using manovacuometry;
- SNIP, using a manovacuometer and nasal plug;
- Symptoms (dyspnea, fatigue, and pain).

Secondary outcomes

- ALSFRS-R (respiratory subscore).
- Rate of disease progression, calculated as the difference between total value of ALSFRS-R and value obtained in the initial assessment divided by time (months) from symptom onset.

Time Frame

We will consider assessments performed before and after interventions.

Search methods for identification of studies

Electronic searches

The research will cover studies in the following databases with no language or date restriction: PUBMED, EMBASE, Cochrane Library, EBSCO, and Physiotherapy Evidence Database (PEDro). The research question will be answered using a designed search strategy following the Cochrane Handbook for Systematic Reviews of Interventions (Lefebvre 2021).

Clinical trials will be searched at the USA National Institutes of Health Ongoing Trials Register, World Health Organization International Clinical Trials Registry Platform, European Union Clinical Trials Register, and Brazilian Clinical Trials Registry. The initial search strategy will be adapted to each database using Boolean operators, OR and AND.

Non-randomized studies identified from search results will be included in the discussion. A manual search in reference lists of all relevant trials and review articles will be conducted for additional references.

Search strategy

Search strategy will be performed according to the Cochrane Library and adapted for each database (Supplemental material)

Data collection and analysis

Selection of studies

Two reviewers (KP and AM) will independently select studies using eligibility criteria. Studies will be selected by title and abstract and using additional

sources. After selection, full texts will be read. Duplicates will be excluded during title and abstract reading or full-text analysis. Decision of reviewers will be blinded, and disagreements will be resolved by discussing with a third reviewer (VR). Decisions will be recorded and managed using the Rayyan QCRI® tool (www.rayyan.ai).

Data extraction and management

The following data will be extracted from selected studies using an extraction form: first author, publication year, study design, sample size, population characteristics, outcome measures, intervention characteristics, statistical results, and main conclusions.

Extraction forms for each study will be filled in an excel spreadsheet by the first reviewer (KP) and verified by a second (AM) reviewer. A third reviewer (VR) will resolve discrepancies. Missing data will be requested from study authors via e-mail.

Quality assessment of included studies

Risk of Bias tool for clinical studies

Risk of bias will be assessed independently by two authors using RoB 2. This tool considers random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data (incomplete outcome data), selective description of the outcome (selective reporting), and other possible biases (other bias).

PRISMA P checklist

The PRISMA P checklist will be applied to maintain transparency, standardize preparation of this systematic review, and accurately summarize information [22].

Data synthesis and analysis

Selected studies will be analyzed and grouped, and results arranged in tables. If possible, a meta-analysis will be performed. Otherwise, data will be reported in a narrative review. Analyzes will be conducted according to intention-to-treat principle (i.e., no missing data). If needed, authors of studies will be contacted to obtain other relevant data.

Grading the quality of evidence

The quality of evidence for all outcomes will be assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) [23] Working Group methodology through risk of bias, consistency, objectivity, accuracy and reported bias. The certainty of evidence will be classified as high, moderate, low or very low.

Patient and public involvement

No patient involved.

Discussion

Clinical trials with patients with ALS often present inconsistent results due to

the rapid progression of the disease and death. Despite knowledge regarding respiratory physiotherapy techniques for patients with ALS, synthesizing and highlighting effective therapies for increasing lung function may help clinical practice; therefore, improving comfort. This systematic review will strengthen the level of evidence using information from randomized controlled trials and may be used as a guideline for the care of patients with ALS.

Review status

The study is at data collection and analysis phase.

Ethics and dissemination

Ethical approval is not required for this systematic review because data are already published and available publicly. This review intends to provide critically and summarized data to produce a practical guideline for respiratory care of patients with ALS.

Author's contributions

KP, research concept and study design, literature review, selection of studies, interpretation of data, data collection, writing of the manuscript, and reviewing.

AAM, selection of studies, data collection, data analysis, and interpretation. E-mail address: fisioanams@gmail.com.

TR, research concept and study design, and reviewing of the manuscript. E-mail address: ribeirotatiana.ufrn@gmail.com.

RTC, reviewing the manuscript. E-mail address: klgorodrigotorres@gmail.com.

RVU, reviewing the manuscript. E-mail address: robertovera@uchile.cl.

GAFF, reviewing the manuscript. E-mail address: fregonezi.guilherme@gmail.com.

VRR, research concept and study design, selection of studies, writing of the manuscript, and reviewing. E-mail address: vanessa.resqueti@ufrn.br.

Funding

This work is supported by the Ministry of Health (TED 132/2018, GESCOM grant number 1.344.512/2015, and CAAE 46072514.8.0000.5292) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil (CAPES) - Funding Code 001.

Vanessa Regiane Resqueti Fregonezi is a fellow of the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) – process number 315580/2018-6.

Guilherme Augusto de Freitas Fregonezi is a fellow of the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) – process number 312876/2018 – 1.

Competing interests: None declared.

References

1 Rusina R, Ridzon P, Kulist'ák P et al. Relationship between ALS and the degree of cognitive impairment, markers of neurodegeneration and predictors for poor outcome. A prospective study. *European Journal of Neurology*, vol. 17, no. 1, pp. 23–30, 2010.

2 Cedarbaum JM, Stambler N, Malta E et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. *Journal of the Neurological Sciences*, Volume 169, Issues 1–2, 1999; 13-21.

3 Rokadia HK, Adams JR, McCarthy K, Aboussouan LS, Mireles-Cabodevila E. Cough Augmentation in a Patient with Neuromuscular Disease. Annals of the American Thoracic Society 2015;12(12):1888-1891.

4 Sarmento A, Resqueti V, Dourado-Júnior M, et al. Effects of Air Stacking Maneuver on Cough Peak Flow and Chest Wall Compartmental Volumes of

Subjects With Amyotrophic Lateral Sclerosis. *Arch Phys Med Rehabil*. 2017;98(11):2237-2246.e1. doi:10.1016/j.apmr.2017.04.015

5 Niedermeyer S, Murn M, Choi PJ. Respiratory Failure in Amyotrophic Lateral Sclerosis. Chest. 2019 Feb;155(2):401-408. doi: 10.1016/j.chest.2018.06.035. Epub 2018 Jul 7. PMID: 29990478.

6 Morgan RK, McNally S, Alexander M, Conroy R, Hardiman O, Costello RW. Use of Sniff nasal-inspiratory force to predict survival in amyotrophic lateral sclerosis. *Am J Respir Crit Care Med*. 2005;171(3):269-274. doi:10.1164/rccm.200403-314OC.

7 Chiò A, Calvo A, Ilardi A, et al. Lower serum lipid levels are related to respiratory impairment in patients with ALS. *Neurology*, vol. 73, no. 20, pp. 1681–1685, 2009.

8 Rokadia HK, Adams JR, McCarthy K, Aboussouan LS, Mireles-Cabodevila E. Cough Augmentation in a Patient with Neuromuscular Disease. Annals of the American Thoracic Society 2015;12(12):1888-1891.

9 Pinto S, Swash M, de Carvalho M. Respiratory exercise in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler*. 2012;13(1):33-43.

10 Benditt JO. Respiratory Care of Patients With Neuromuscular Disease. Respir Care. 2019 Jun;64(6):679-688. doi: 10.4187/respcare.06827. PMID: 31110036.

11 Laghi F, Tobin MJ. Disorders of the respiratory muscles. Am J Respir Crit Care Med 2003; 168:10-48.

12 Kravitz RM. Airway clearance in Duchenne muscular dystrophy. *Pediatrics* 2009;123(Suppl 4):S231-235.

13 Smith JA, Aliverti A, Quaranta M, et al. Chest wall dynamics during voluntary and induced cough in healthy volunteers. *J Physiol* 2012;590:563-74.

14 Lo Mauro A, Aliverti A. Physiology of respiratory disturbances in muscular dystrophies. *Breathe (Sheff)* 2016;12:318-27.

15 Miller RG, Brooks BR, Swain-Eng R, et al. Quality improvement in neurology: amyotrophic lateral sclerosis quality measures. Report of the quality measurement and reporting subcommittee of the American Academy of Neurology. *Neurology.* 2013;81(24):2136–2140

16 National Institute for Health and Care Excellence . *Motor Neurone Disease: Assessment and Management.* London, UK: Clinical Guideline NG42, NICE; 2016.

17 Bello-Haas VD. Physical therapy for individuals with amyotrophic lateral sclerosis: current insights. *Degener Neurol Neuromuscul Dis*. 2018;8:45-54. Published 2018 Jul 16. doi:10.2147/DNND.S146949

18 Cleary S, Misiaszek JE, Kalra S, Wheeler S, Johnston W. The effects of lung volume recruitment on coughing and pulmonary function in patients with ALS. *Amyotroph Lateral Scler Frontotemporal Degener.* 2013;14(2):111–115.

19 Sancho, J., Servera, E., Bañuls, P., & Marín, J. (2017). Effectiveness of assisted and unassisted cough capacity in amyotrophic lateral sclerosis patients. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, *18*(7–8), 498–504. https://doi.org/10.1080/21678421.2017.1335324

20 Kaminska M, Browman F, Trojan DA, Genge A, Benedetti A, Petrof BJ. Feasibility of lung volume recruitment in early neuromuscular weakness: a comparison between amyotrophic lateral sclerosis, myotonic dystrophy, and postpolio syndrome. *Phys Med Rehabil.* 2015;7(7):677–684.

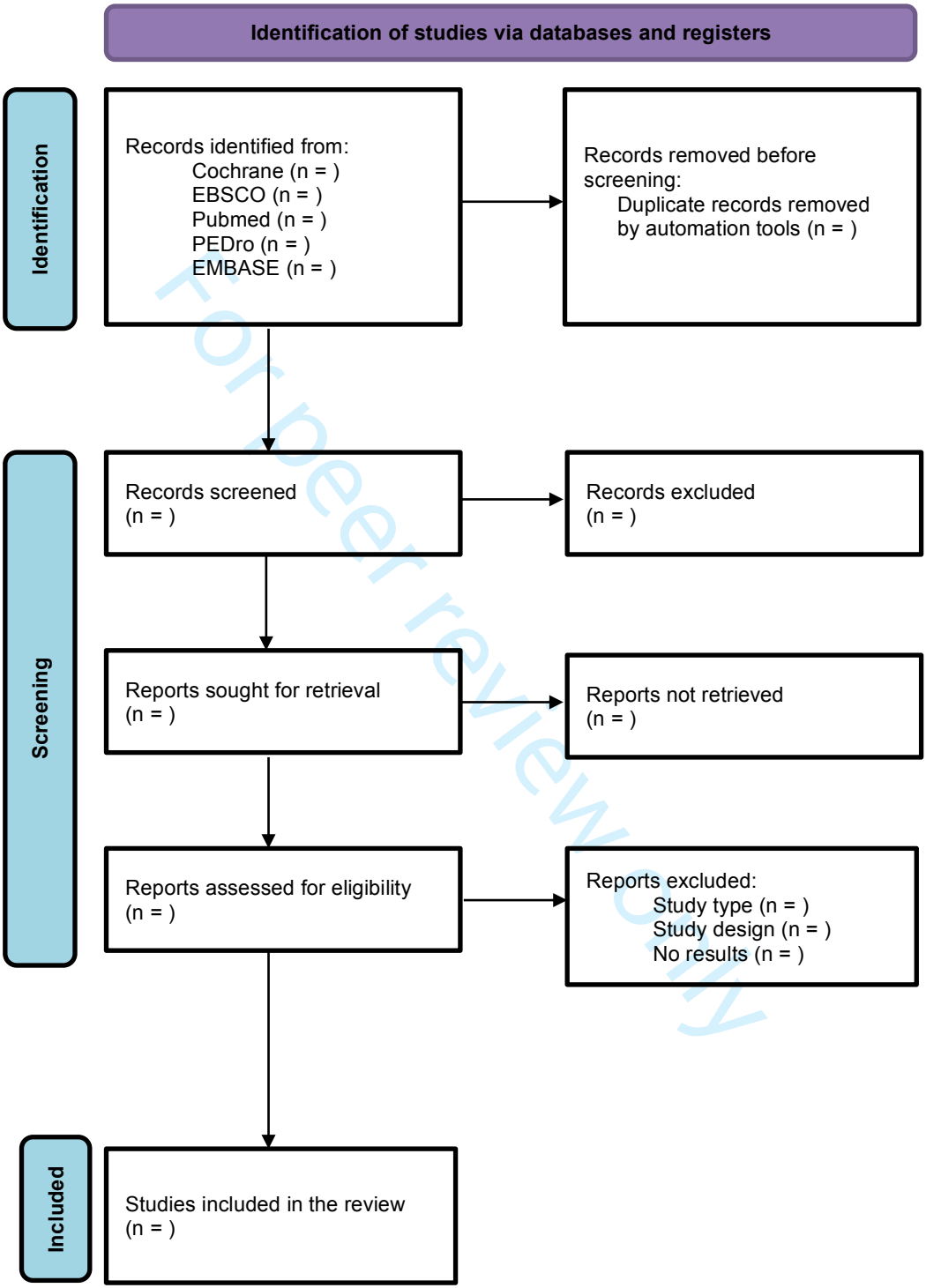
21 Macpherson CE, Bassile CC. Pulmonary physical therapy techniques to enhance survival in amyotrophic lateral sclerosis: a systematic review. *J Neurol Phys Ther.* 2016;40(3):165–175.

22 Moher, D., Shamseer, L., Clarke, M. *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* **4,** 1 (2015). https://doi.org/10.1186/2046-4053-4-1

23 Guyatt G, Oxman AD, Akl EA, et al. . Grade guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94. 10.1016/j.jclinepi.2010.04.026

Figure Legend

Figure 1 - Flow diagram for study selection based on PRISMA guidelines.



Supplemental

(cough assist OR cough assist techniques OR cough assistance OR cough assistance ventilation OR cough assisted OR cough assisting OR air stacking OR air stacking assisted OR air stacking exercise OR air stacking maneuvers OR air stacking group OR Therapy, Respiratory OR Respiratory Therapies OR Inhalation Therapy OR Inhalation Therapies OR Exercise, Breathing OR Respiratory Muscle Training OR Therapy, Exercise OR Exercise Therapies OR Rehabilitation Exercise OR Rehabilitation Exercises OR Modalities, Physical Therapy OR Physical Therapy Modality OR Physiotherapy OR Physiotherapies OR Physical Therapy Techniques OR Physical Therapy Technique OR Group Physiotherapy OR Group Physiotherapies OR Physical Therapy OR Physical Therapies OR Neurological Physiotherapy OR Neurophysiotherapy)

AND (Amyotrophic lateral sclerosis OR ALS Amyotrophic Lateral Sclerosis OR ALS Amyotrophic Lateral Sclerosis OR Amyotrophic Lateral Sclerosis Parkinsonism Dementia Complex 1 OR Amyotrophic Lateral Sclerosis With Dementia OR Amyotrophic Lateral Sclerosis, Guam Form OR Amyotrophic Lateral Sclerosis, Parkinsonism Dementia Complex of Guam OR Amyotrophic Lateral Sclerosis-Parkinsonism-Dementia Complex 1 OR Dementia With Amyotrophic Lateral Sclerosis OR Gehrig Disease OR Gehrig's Disease OR Guam Disease OR Lou Gehrig Disease OR Lou Gehrig's Disease OR Motor Neuron Disease, Amyotrophic Lateral Sclerosis OR Motor Neuron Diseases OR Motor System Disease OR Motor System Diseases OR Neuron Disease, Motor OR Lateral Scleroses OR Primary Lateral Scleroses OR Primary

Lateral Sclerosis OR Scleroses, Lateral OR Sclerosis, Lateral OR Upper Motor Neuron Disease OR Secondary Motor Neuron Disease OR Lower Motor Neuron Disease).

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Pages where item is reported
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Abstract, page 4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title, pages 10, 11
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 14
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Introdution pages 5, 6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Pages 6, 7, 8, 9, 10

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 11 / Appendix 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 11
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Pages 9, 10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Pages 9, 10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Risk of Bias tool for clinical studies, page 12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	-
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Effects of respiratory physiotherapy in patients with amyotrophic lateral sclerosis: protocol for a systematic review of randomised controlled trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061624.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Apr-2022
Complete List of Authors:	Pondofe, Karen; Universidade Federal do Rio Grande do Norte Centro de Ciências da Saúde, aboratório de Inovação Tecnológica em Reabilitação e PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH) Marcelino, Ana; Universidade Federal do Rio Grande do Norte, aboratório de Inovação Tecnológica em Reabilitação e PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH) Ribeiro, Tatiana Souza; Federal University of Rio Grande do Norte, Departamento de Fisioterapia e Laboratório de Inovação Tecnológica em Saúde (LAIS), Hospital Universitário Onofre Lopes (HUOL), Empresa Brasileira de Serviços Hospitalares (EBSERH) Torres-Castro, Rodrigo; Universidad de Chile, Physiotherapy; Universidad de Chile Vera-Uribe, Roberto; University of Chile, Department of Physical Therapy Fregonezi, Guilherme; Universidade Federal do Rio Grande do Norte, Laboratório de Inovação Tecnológica em Reabilitação e PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH) Resqueti, Vanessa; Universidade Federal do Rio Grande do Norte, Fisioterapia, Laboratório de Inovação Tecnológica em Reabilitação e PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH)
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Motor neurone disease < NEUROLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Neuromuscular disease < NEUROLOGY, REHABILITATION MEDICINE

Effects of respiratory physiotherapy in patients with amyotrophic lateral sclerosis: protocol for a systematic review of randomised controlled trials

Karen Pondofe[1,2,3]*, Ana Aline Marcelino[1,2,3], Tatiana Ribeiro[3,4], Rodrigo Torres-Castro[5,6], Roberto Vera-Uribe[5,6], Guilherme Fregonezi[1,2,6], Vanessa R Resqueti[1,2,6]

[1] Laboratório de Inovação Tecnológica em Reabilitação, Departamento de Fisioterapia, Universidade Federal do Rio Grande do Norte (UFRN), Natal, Campus Universitário Central, Natal, Rio Grande do Norte, Brazil.
[2] PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH), Universidade Federal do Rio Grande do Norte (UFRN), Natal, Rio Grande do Norte, Brazil.
[3] Departamento de Fisioterapia da Universidade Federal do Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil.
[4] Laboratório de Inovação Tecnológica em Saúde (LAIS), Hospital Universitário Onofre Lopes (HUOL), Empresa Brasileira de Serviços Hospitalares (EBSERH), Universidade Federal do Rio Grande do Norte (UFRN), Natal, Rio Grande do Norte, Brazil.
[5] Department of Physical Therapy, Faculty of Medicine, University of Chile, Santiago, Chile.
[6] International Physical Therapy Research Network (PhysioEvidence).

* Corresponding author: Karen Pondofe. Affiliations: Laboratório de Inovação Tecnológica em Reabilitação, Departamento de Fisioterapia, Universidade Federal do Rio Grande do Norte (UFRN). PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH), Universidade Federal do Rio Grande do Norte (UFRN), Natal, Rio Grande do Norte, Brazil.
Email address: karenpondofe@yahoo.com.br

Word Count: 1658

ABSTRACT

Introduction: Respiratory muscle weakness and ventilatory failure are common complications in patients with amyotrophic lateral sclerosis (ALS) and may lead to death. Respiratory physiotherapy may improve lung function in this population. This study aims to investigate the effects of respiratory physiotherapy on lung function, cough efficacy and functional status of patients with ALS. **Methods and analysis:** A protocol was published on the International prospective register of systematic reviews (PROSPERO). The research will cover randomised controlled trials (RCTs), with no language or publication date restriction, available in the following databases: MEDLINE/PUBMED, EMBASE, Cochrane Library, Web of Science, and Physiotherapy Evidence Database. The research question will be answered using a search strategy adapted for each database. Searches in databases will be conducted from January 2021 to December 2022. Two authors using the Cochrane risk-of-bias tool for randomised trials version 2 and grading of recommendations assessment, development and evaluation, respectively, will assess risk of bias and quality of evidence independently. According to the results obtained, data will be reported as a meta-analysis or a narrative report. **Ethics and dissemination:** No previous ethical approval is required for this publication since data used is already published. Results of this review will be disclosed via peer-reviewed publications and conference presentations. PROSPERO registration number CRD42021251842.

Keywords: Amyotrophic lateral sclerosis; forced vital capacity; inspiratory muscle weakness; functional capacity; respiratory insufficiency; nasal inspiratory pressure

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study presents high-level evidence using randomised controlled trials.
- This protocol allows for peer review and reduces the possibility of bias and duplicates.
- The protocol followed the PRISMA-P guidelines, and we will use the GRADE system to analyze the quality of the evidence.
- The limited number of studies available may limit the certainty of the evidence from this systematic review.

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized by loss of cortical, brainstem, and spinal motor neurons. The average survival time from symptom onset is 3 to 5 years; however, survival may be longer in patients with slow disease progression [1].

Progressive respiratory muscle weakness is one of the main complications affecting patients with ALS [2]. Lung volume reduces over time and leads to ineffective cough and worsening prognosis due to accumulation of secretions [3]. Respiratory failure is primarily determined by impaired inspiratory muscle strength associated with loss of motor unit of intercostal and axial muscles [4].

Forced vital capacity (FVC), maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP) are measures of respiratory function easily performed and monitored in the clinical environment. FVC is widely used in patients with ALS and associates with disease progression and survival (FVC of < 50% indicates the beginning of respiratory failure). Sniff nasal inspiratory pressure (SNIP) is considered a more accessible alternative than MIP for monitoring respiratory muscle strength [5]. It provides important prognostic information (SNIP of < 40 cmH2O is associated with an average survival of 6 months), and predicts the nocturnal desaturation and respiratory failure in patients with ALS [6].

Decreased physical function negatively impacts activities of daily living during disease progression. The revised ALS Functional Rating Scale (ALSFRS-R) is strongly related to ALS survival and prognosis is used to assess and

monitor the functional status of patients with ALS over time and adds the breathing assessment sub-category [2, 7].

Respiratory system dysfunction ends up being a terminal event for most of these patients [8, 9], with a reduction in total lung capacity, vital capacity and functional residual capacity [10]. Loss of phrenic nerve function causes diaphragm weakness, which can lead to further complications. Despite the different presentations, most patients have speech impairment and airway clearance due to reduced bulbar muscle coordination [11].

The combination of inspiratory muscle weakness and reduced chest wall compliance limits the amount of volume needed for an effective cough. Inspiratory capacity represents the volume inspired until the end of the inspiratory phase of cough and is considered the most determining factor for peak cough flow (PCF) (i.e., affects length of expiratory muscle and efficiency of subsequent contraction). Also, adequate pressures to develop compressive forces and clear airway secretions are not achieved in the presence of glottic insufficiency. [12, 13, 14]

Impaired expiratory muscle contraction also decreases the ability to cough and clear secretions. Physiotherapists should assess and monitor vital capacity, MIP, SNIP, or peak expiratory cough flow of patients with ALS at least every three months [15, 16]. Physiotherapeutic interventions used in individuals with expiratory muscle weakness and secretion retention are lung volume recruitment, and airway clearance techniques with breath stacking, air stacking, and manually assisted coughing [17, 18, 19, 20].

In addition, inspiratory muscle training, lung volume recruitment training, and mechanical insufflation-exsufflation may also improve survival and should be

included in the overall management of ALS [16, 21].

This systematic review will investigate the effects of respiratory physiotherapy on lung function, cough efficacy and functional status of patients with ALS.

REVIEW QUESTION

"What are the effects of respiratory physiotherapy on lung function, cough efficacy and functional status of patients with ALS?"

METHODS AND ANALYSIS

The study will be conducted according to the Preferred reporting items for systematic reviews and meta-analysis guidelines (PRISMA-P) [22]. Searches in databases will be conducted from January 2021 to December 2022. The protocol for this review was submitted to the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42021251842.

Eligibility criteria

Randomised controlled trials (RCTs) performed with adult patients, all ages, of both genders and diagnosed with definite, probable, probable laboratory-supported, possible, or suspected ALS will be included if full-text or sufficient information about respiratory therapy and results are present. Non-randomized studies found during the search will be considered for the discussion section. Main steps of the search phase will be reported using a PRISMA flow diagram (Figure 1). Studies performed with patients with

neurodegenerative, cardiac, or respiratory diseases associated will be excluded.

[Insert figure 1]

Types of interventions

Intervention

Non-invasive respiratory physiotherapy techniques: breathing exercises, respiratory muscle training, air stacking, lung volume recruitment training, non-invasive ventilation, manually assisted cough, or mechanical insufflation-exsufflation.

Comparators

Placebo or any combination of other interventions designated as standard treatment or usual conventional care or no intervention will be considered for the control group.

Types of outcome measures

Primary outcomes

- Forced Vital capacity (FVC)
- Maximal respiratory pressure (MIP and MEP)

Secondary outcomes

- Peak cough flow

- Sniff nasal inspiratory pressure (SNIP)
- Functional status (ALSFRS-R)

Time Frame

We will consider assessments performed before and after interventions for a minimum of three weeks. We will perform timeline analyzes of the evaluated outcomes according to the results found with a maximum of 1 year of follow-up.

Search methods for identification of studies

Electronic searches

The research will cover studies in the following databases with no language or date restriction: MEDLINE/PUBMED, EMBASE, Cochrane Library, Web of Science, and Physiotherapy Evidence Database (PEDro). The research question will be answered using a designed search strategy following the Cochrane Handbook for Systematic Reviews of Interventions (Lefebvre 2021). Clinical trials will be searched at the USA National Institutes of Health Ongoing Trials Register, World Health Organization International Clinical Trials Registry Platform, European Union Clinical Trials Register, and Brazilian Clinical Trials Registry. The initial search strategy will be adapted to each database using Boolean operators, OR and AND.

Non-randomized studies identified from search results will be included in the discussion. A manual search in reference lists of all relevant trials and review articles will be conducted for additional references.

Search strategy

Search strategy will be performed according to the Cochrane Library and adapted for each database (Supplemental material)

Data collection and analysis

Selection of studies

Two reviewers (KP and AM) will independently select studies using eligibility criteria. Studies will be selected by title and abstract and using additional sources. After selection, full texts will be read. Duplicates will be excluded during title and abstract reading or full-text analysis. Decision of reviewers will be blinded, and disagreements will be resolved by discussing with a third reviewer (VR). Decisions will be recorded and managed using the Rayyan QCRI® tool (www.rayyan.ai).

Data extraction and management

The following data will be extracted from selected studies using an extraction form: first author, publication year, study design, sample size, population characteristics, outcome measures, intervention characteristics, statistical results, and main conclusions.

Extraction forms for each study will be filled in an excel spreadsheet by the first reviewer (KP) and verified by a second (AM) reviewer. A third reviewer (VR) will resolve discrepancies. Missing data will be requested from study authors by email.

Quality assessment of included studies

Risk of Bias tool for clinical studies

Risk of bias will be assessed independently by two authors using RoB 2. This tool considers random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data (incomplete outcome data), selective description of the outcome (selective reporting), and other possible biases (other bias).

PRISMA P checklist

The PRISMA P checklist will be applied to maintain transparency, standardize preparation of this systematic review, and accurately summarize information [22].

Data synthesis and analysis

Selected studies will be analyzed and grouped, and results will be arranged in tables. Analyzes will be conducted according to the intention-to-treat principle (i.e., no missing data). If needed, authors of studies will be contacted to obtain other relevant data. We will base the analyses on available data from all included trials relevant to the comparisons and outcomes of interest. We will include the trials with the most complete data for each outcome. Where data are available from more than one study assessing the same outcome, we will undertake meta-analyses; otherwise, data will be reported in a narrative

review. We will use a fixed-effect model to calculate pooled estimates and 95% confidence intervals (CIs). If significant heterogeneity exists, we will use a random-effects model. We will use means and standard deviations (SD) to calculate the mean difference (MD) and 95% CI for continuous variables. For categorical outcomes, we will relate the numbers reporting an outcome to the numbers at risk in each group to calculate a risk ratio (RR) and 95% CI. If similar outcomes are reported on different scales, we will calculate the standardised mean difference (SMD). If data to calculate RRs or MDs are not given, we will utilise the most detailed numerical data available to calculate the actual numbers or means and SD (for example, test statistics, p values).

Grading the quality of evidence

The quality of evidence for all outcomes will be assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) [23] Working Group methodology through risk of bias, consistency, objectivity, accuracy and reported bias. The certainty of evidence will be classified as high, moderate, low or very low.

Patient and public involvement

No patient involved.

Discussion

Clinical trials with patients with ALS often present inconsistent results due to the rapid progression of the disease and death. Despite knowledge regarding respiratory physiotherapy techniques for patients with ALS, synthesizing and highlighting effective therapies for increasing lung function may help clinical

practice; therefore, improving comfort. This systematic review will strengthen the level of evidence using information from randomized controlled trials and may be used as a guideline for the care of patients with ALS.

Limitations

Possible limitations can be found, such as data heterogeneity, due to differences in intervention protocols and ALS diagnosis subtypes. Impossibility of performing meta-analysis and possible methodological biases since the population studied is highly chronic and susceptible to exacerbations and deaths.

Review status

The study is in the data collection and analysis phase.

Ethics and dissemination

Ethical approval is not required for this systematic review because data are already published and available publicly. This review intends to provide critically and summarized data to produce a practical guideline for respiratory care of patients with ALS.

Author's contributions

KP, research concept and study design, literature review, selection of studies, interpretation of data, data collection, writing of the manuscript, and reviewing.

AAM, selection of studies, data collection, data analysis, and interpretation. E-mail address: fisioanams@gmail.com.

TR, research concept and study design, and reviewing of the manuscript. E-mail address: ribeirotatiana.ufrn@gmail.com.

RTC, reviewing the manuscript. E-mail address: klgorodrigotorres@gmail.com.

RVU, reviewing the manuscript. E-mail address: robertovera@uchile.cl.

GAFF, reviewing the manuscript. E-mail address: fregonezi.guilherme@gmail.com.

VRR, research concept and study design, selection of studies, writing of the manuscript, and reviewing. E-mail address: vanessa.resqueti@ufrn.br.

Funding

This work is supported by the Ministry of Health (TED 132/2018, GESCOM grant number 1.344.512/2015, and CAAE 46072514.8.0000.5292) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil (CAPES) - Funding Code 001.

Vanessa Regiane Resqueti Fregonezi is a fellow of the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) – process number 315580/2018-6.

Guilherme Augusto de Freitas Fregonezi is a fellow of the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) – process number 312876/2018 – 1.

Competing interests: None declared.

References

1 Rusina R, Ridzon P, Kulist'ák P et al. Relationship between ALS and the degree of cognitive impairment, markers of neurodegeneration and predictors for poor outcome. A prospective study. *European Journal of Neurology*, vol. 17, no. 1, pp. 23–30, 2010.

2 Cedarbaum JM, Stambler N, Malta E et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. *Journal of the Neurological Sciences*, Volume 169, Issues 1–2, 1999; 13-21.

3 Rokadia HK, Adams JR, McCarthy K, Aboussouan LS, Mireles-Cabodevila E. Cough Augmentation in a Patient with Neuromuscular Disease. Annals of the American Thoracic Society 2015;12(12):1888-1891.

4 Sarmento A, Resqueti V, Dourado-Júnior M, et al. Effects of Air Stacking Maneuver on Cough Peak Flow and Chest Wall Compartmental Volumes of Subjects With Amyotrophic Lateral Sclerosis. *Arch Phys Med Rehabil*. 2017;98(11):2237-2246.e1. doi:10.1016/j.apmr.2017.04.015

5 Niedermeyer S, Murn M, Choi PJ. Respiratory Failure in Amyotrophic Lateral Sclerosis. Chest. 2019 Feb;155(2):401-408. doi: 10.1016/j.chest.2018.06.035. Epub 2018 Jul 7. PMID: 29990478.

6 Morgan RK, McNally S, Alexander M, Conroy R, Hardiman O, Costello RW. Use of Sniff nasal-inspiratory force to predict survival in amyotrophic lateral sclerosis. *Am J Respir Crit Care Med*. 2005;171(3):269-274. doi:10.1164/rccm.200403-314OC.

7 Chiò A, Calvo A, Ilardi A, et al. Lower serum lipid levels are related to respiratory impairment in patients with ALS. *Neurology*, vol. 73, no. 20, pp. 1681–1685, 2009.

8 Rokadia HK, Adams JR, McCarthy K, Aboussouan LS, Mireles-Cabodevila E. Cough Augmentation in a Patient with Neuromuscular Disease. Annals of the American Thoracic Society 2015;12(12):1888-1891.

9 Pinto S, Swash M, de Carvalho M. Respiratory exercise in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler*. 2012;13(1):33-43.

10 Benditt JO. Respiratory Care of Patients With Neuromuscular Disease. Respir Care. 2019 Jun;64(6):679-688. doi: 10.4187/respcare.06827. PMID: 31110036.

11 Laghi F, Tobin MJ. Disorders of the respiratory muscles. Am J Respir Crit Care Med 2003; 168:10-48.

12 Kravitz RM. Airway clearance in Duchenne muscular dystrophy. *Pediatrics* 2009;123(Suppl 4):S231-235.

13 Smith JA, Aliverti A, Quaranta M, et al. Chest wall dynamics during voluntary and induced cough in healthy volunteers. *J Physiol* 2012;590:563-74.

14 Lo Mauro A, Aliverti A. Physiology of respiratory disturbances in muscular dystrophies. *Breathe (Sheff)* 2016;12:318-27.

15 Miller RG, Brooks BR, Swain-Eng R, et al. Quality improvement in neurology: amyotrophic lateral sclerosis quality measures. Report of the quality measurement and reporting subcommittee of the American Academy of Neurology. *Neurology.* 2013;81(24):2136–2140

16 National Institute for Health and Care Excellence . *Motor Neurone Disease: Assessment and Management.* London, UK: Clinical Guideline NG42, NICE; 2016.

17 Bello-Haas VD. Physical therapy for individuals with amyotrophic lateral sclerosis: current insights. *Degener Neurol Neuromuscul Dis*. 2018;8:45-54. Published 2018 Jul 16. doi:10.2147/DNND.S146949

18 Cleary S, Misiaszek JE, Kalra S, Wheeler S, Johnston W. The effects of lung volume recruitment on coughing and pulmonary function in patients with ALS. *Amyotroph Lateral Scler Frontotemporal Degener.* 2013;14(2):111–115.

19 Sancho, J., Servera, E., Bañuls, P., & Marín, J. (2017). Effectiveness of assisted and unassisted cough capacity in amyotrophic lateral sclerosis patients. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, *18*(7–8), 498–504. https://doi.org/10.1080/21678421.2017.1335324

20 Kaminska M, Browman F, Trojan DA, Genge A, Benedetti A, Petrof BJ. Feasibility of lung volume recruitment in early neuromuscular weakness: a comparison between amyotrophic lateral sclerosis, myotonic dystrophy, and postpolio syndrome. *Phys Med Rehabil.* 2015;7(7):677–684.

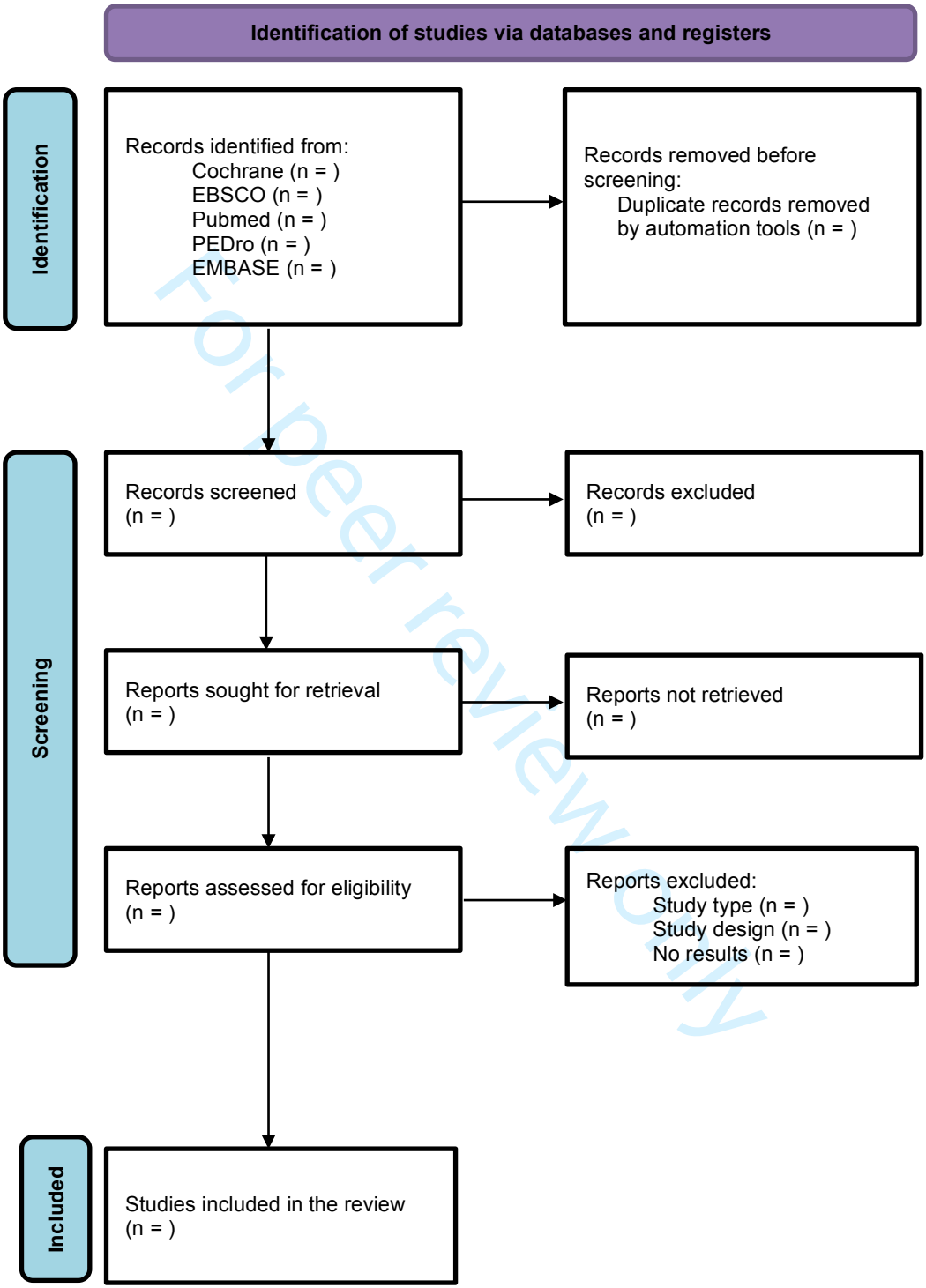
21 Macpherson CE, Bassile CC. Pulmonary physical therapy techniques to enhance survival in amyotrophic lateral sclerosis: a systematic review. *J Neurol Phys Ther.* 2016;40(3):165–175.

22 Moher, D., Shamseer, L., Clarke, M. *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* **4,** 1 (2015). https://doi.org/10.1186/2046-4053-4-1

23 Guyatt G, Oxman AD, Akl EA, et al. . Grade guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94. 10.1016/j.jclinepi.2010.04.026

Figure Legend

Figure 1 - Flow diagram for study selection based on PRISMA guidelines.



Supplemental

(cough assist OR cough assist techniques OR cough assistance OR cough assistance ventilation OR cough assisted OR cough assisting OR air stacking OR air stacking assisted OR air stacking exercise OR air stacking maneuvers OR air stacking group OR Therapy, Respiratory OR Respiratory Therapies OR Inhalation Therapy OR Inhalation Therapies OR Exercise, Breathing OR Respiratory Muscle Training OR Therapy, Exercise OR Exercise Therapies OR Rehabilitation Exercise OR Rehabilitation Exercises OR Modalities, Physical Therapy OR Physical Therapy Modality OR Physiotherapy OR Physiotherapies OR Physical Therapy Techniques OR Physical Therapy Technique OR Group Physiotherapy OR Group Physiotherapies OR Physical Therapy OR Physical Therapies OR Neurological Physiotherapy OR Neurophysiotherapy)

AND (Amyotrophic lateral sclerosis OR ALS Amyotrophic Lateral Sclerosis OR ALS Amyotrophic Lateral Sclerosis OR Amyotrophic Lateral Sclerosis Parkinsonism Dementia Complex 1 OR Amyotrophic Lateral Sclerosis With Dementia OR Amyotrophic Lateral Sclerosis, Guam Form OR Amyotrophic Lateral Sclerosis, Parkinsonism Dementia Complex of Guam OR Amyotrophic Lateral Sclerosis-Parkinsonism-Dementia Complex 1 OR Dementia With Amyotrophic Lateral Sclerosis OR Gehrig Disease OR Gehrig's Disease OR Guam Disease OR Lou Gehrig Disease OR Lou Gehrig's Disease OR Motor Neuron Disease, Amyotrophic Lateral Sclerosis OR Motor Neuron Diseases OR Motor System Disease OR Motor System Diseases OR Neuron Disease, Motor OR Lateral Scleroses OR Primary Lateral Scleroses OR Primary

Lateral Sclerosis OR Scleroses, Lateral OR Sclerosis, Lateral OR Upper Motor Neuron Disease OR Secondary Motor Neuron Disease OR Lower Motor Neuron Disease).

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Pages where item is reported
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Abstract, page 4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title, pages 10, 11
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 14
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Introdution pages 5, 6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Pages 6, 7, 8, 9, 10

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 11 / Appendix 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 11
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Pages 9, 10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Pages 9, 10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Risk of Bias tool for clinical studies, page 12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	-
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.