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# BMJ Open

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

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Manuscripts

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3 Effects of respiratory physiotherapy in patients with amyotrophic lateral  
4 sclerosis: a systematic review protocol  
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## 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.

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## 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<sub>2</sub>O is associated with an average survival of 6 months), and accurately predicts nocturnal desaturation and respiratory failure in patients with ALS [6].

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3 Decreased physical function negatively impacts activities of daily living during  
4 disease progression. The revised ALS Functional Rating Scale (ALSF<sub>RS</sub>-R)  
5 is strongly related to ALS survival and prognosis is used to assess and  
6 monitor the functional status of patients with ALS over time. It assesses  
7 speech, salivation, swallowing, handwriting, cutting food and handling  
8 utensils, dressing and hygiene, turning in bed and adjusting bed linen,  
9 walking, climbing stairs, and adds the breathing assessment sub-category [2,  
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22 Respiratory system dysfunction is the terminal event for most patients with  
23 ALS [8, 9]. Respiratory muscle weakness reduce total lung capacity, vital  
24 capacity, and functional residual capacity and the measurements of  
25 respiratory muscle strength are essential for long-term monitoring of these  
26 patients [10]. Loss of phrenic nerve function causes diaphragm weakness,  
27 which may lead to further complication. Despite different presentations, most  
28 patients present impaired speaking and airway clearance due to reduced  
29 bulbar muscle coordination [11].  
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41 The combination of inspiratory muscle weakness and reduced chest wall  
42 compliance limits the amount of volume needed for an effective cough.  
43 Inspiratory capacity represents the volume inspired until the end of the  
44 inspiratory phase of cough and is considered the most determining factor for  
45 peak cough flow (i.e., affects length of expiratory muscle and efficiency of  
46 subsequent contraction). Also, adequate pressures to develop compressive  
47 forces and clear airway secretions are not achieved in the presence of glottic  
48 insufficiency. [12, 13, 14]  
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59 Impaired expiratory muscle contraction also decreases the ability to cough  
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3 and clear secretions. Physiotherapists should assess and monitor vital  
4 capacity, MIP, SNIP, or peak expiratory cough flow of patients with ALS at  
5 least every three months. [15, 16] physiotherapeutic interventions used in  
6 individuals with expiratory muscle weakness and secretion retention are lung  
7 volume recruitment, and airway clearance techniques with breath stacking,  
8 air stacking, and manually assisted coughing. [17, 18, 19, 20]  
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17 In addition, inspiratory muscle training, lung volume recruitment training,  
18 manually assisted coughing, and mechanical insufflation-exsufflation may also  
19 improve survival and should be included in the overall management of ALS.  
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24 [16, 21]  
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26 This systematic review will investigate the effects of respiratory physiotherapy  
27 on forced expiratory volume one second (FEV1), the forced vital capacity  
28 (FVC), peak cough flow, inspiratory reserve volume, and maximal respiratory  
29 pressures of patients with ALS and monitor the variables symptom, ALSFRS-  
30 R, and rate of disease progression.  
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## 40 **REVIEW QUESTION**

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43 “What are the effects of respiratory physiotherapy on lung function (capacities,  
44 volumes, and respiratory muscle strength), cough efficacy, and symptoms of  
45 patients with ALS?”  
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## 50 **METHODS AND ANALYSIS**

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54 The study will be conducted according to the Preferred Reporting Items for  
55 Systematic Reviews and Meta-Analysis guidelines (PRISMA-P) [22].  
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57 Searches in databases will be conducted from January 2021 to December  
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3 2022. The protocol for this review was submitted to the International  
4 Prospective Register of Systematic Reviews (CRD42021251842).  
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## 8 **Eligibility criteria**

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

### 38 **Intervention**

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

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

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20 The following data will be extracted from selected studies using an extraction  
21 form: first author, publication year, study design, sample size, population  
22 characteristics, outcome measures, intervention characteristics, statistical  
23 results, and main conclusions.  
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32 Extraction forms for each study will be filled in an excel spreadsheet by the  
33 first reviewer (KP) and verified by a second (AM) reviewer. A third reviewer  
34 (VR) will resolve discrepancies. Missing data will be requested from study  
35 authors via e-mail.  
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### 44 **Quality assessment of included studies**

#### 45 **Risk of Bias tool for clinical studies**

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

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

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22 The study is at data collection and analysis phase.  
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### 25 **Ethics and dissemination**

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28 Ethical approval is not required for this systematic review because data are  
29 already published and available publicly. This review intends to provide  
30 critically and summarized data to produce a practical guideline for respiratory  
31 care of patients with ALS.  
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### 38 **Author's contributions**

39  
40 KP, research concept and study design, literature review, selection of studies,  
41 interpretation of data, data collection, writing of the manuscript, and reviewing.  
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**Competing interests:** None declared.

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8 Figure 1 - Flow diagram for study selection based on PRISMA guidelines.  
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**Identification of studies via databases and registers**

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**Identification**

Records identified from:  
Cochrane (n = )  
EBSCO (n = )  
Pubmed (n = )  
PEDro (n = )  
EMBASE (n = )

Records removed before screening:  
Duplicate records removed by automation tools (n = )

**Screening**

Records screened (n = )

Records excluded (n = )

Reports sought for retrieval (n = )

Reports not retrieved (n = )

Reports assessed for eligibility (n = )

Reports excluded:  
Study type (n = )  
Study design (n = )  
No results (n = )

**Included**

Studies included in the review (n = )

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3 Supplemental  
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6 (cough assist OR cough assist techniques OR cough assistance OR cough  
7 assistance ventilation OR cough assisted OR cough assisting OR air stacking  
8 OR air stacking assisted OR air stacking exercise OR air stacking maneuvers  
9 OR air stacking group OR Therapy, Respiratory OR Respiratory Therapies  
10 OR Inhalation Therapy OR Inhalation Therapies OR Exercise, Breathing OR  
11 Respiratory Muscle Training OR Therapy, Exercise OR Exercise Therapies  
12 OR Rehabilitation Exercise OR Rehabilitation Exercises OR Modalities,  
13 Physical Therapy OR Physical Therapy Modality OR Physiotherapy OR  
14 Physiotherapies OR Physical Therapy Techniques OR Physical Therapy  
15 Technique OR Group Physiotherapy OR Group Physiotherapies OR Physical  
16 Therapy OR Physical Therapies OR Neurological Physiotherapy OR  
17 Neurophysiotherapy)  
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35 AND (Amyotrophic lateral sclerosis OR ALS Amyotrophic Lateral Sclerosis  
36 OR ALS Amyotrophic Lateral Sclerosis OR Amyotrophic Lateral Sclerosis  
37 Parkinsonism Dementia Complex 1 OR Amyotrophic Lateral Sclerosis With  
38 Dementia OR Amyotrophic Lateral Sclerosis, Guam Form OR Amyotrophic  
39 Lateral Sclerosis, Parkinsonism Dementia Complex of Guam OR Amyotrophic  
40 Lateral Sclerosis-Parkinsonism-Dementia Complex 1 OR Dementia With  
41 Amyotrophic Lateral Sclerosis OR Gehrig Disease OR Gehrig's Disease OR  
42 Guam Disease OR Lou Gehrig Disease OR Lou Gehrig's Disease OR Motor  
43 Neuron Disease, Amyotrophic Lateral Sclerosis OR Motor Neuron Diseases  
44 OR Motor System Disease OR Motor System Diseases OR Neuron Disease,  
45 Motor OR Lateral Scleroses OR Primary Lateral Scleroses OR Primary  
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3 Lateral Sclerosis OR Scleroses, Lateral OR Sclerosis, Lateral OR Upper  
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5 Motor Neuron Disease OR Secondary Motor Neuron Disease OR Lower  
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8 Motor Neuron Disease).  
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For peer review only

**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
<b>ADMINISTRATIVE INFORMATION</b>			
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	
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	Introduction 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
<b>METHODS</b>			
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 $\tau$ )	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 where 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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-061624.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Apr-2022
Complete List of Authors:	<p>Pondofe, Karen; Universidade Federal do Rio Grande do Norte Centro de Ciências da Saúde, laboratório de Inovação Tecnológica em Reabilitação e PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH)</p> <p>Marcelino, Ana; 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)</p> <p>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)</p> <p>Torres-Castro, Rodrigo; Universidad de Chile, Physiotherapy; Universidad de Chile</p> <p>Vera-Uribe, Roberto; University of Chile, Department of Physical Therapy</p> <p>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)</p> <p>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)</p>
<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Motor neurone disease < NEUROLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Neuromuscular disease < NEUROLOGY, REHABILITATION MEDICINE

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3 Effects of respiratory physiotherapy in patients with amyotrophic lateral  
4 sclerosis: protocol for a systematic review of randomised controlled trials  
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9 Karen Pondofe<sup>1,2,3\*</sup>, Ana Aline Marcelino<sup>1,2,3</sup>, Tatiana Ribeiro<sup>3,4</sup>, Rodrigo  
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13 Resqueti<sup>1,2,6</sup>  
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60 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 cmH<sub>2</sub>O 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

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2  
3 monitor the functional status of patients with ALS over time and adds the  
4 breathing assessment sub-category [2, 7].  
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7  
8 Respiratory system dysfunction ends up being a terminal event for most of  
9 these patients [8, 9], with a reduction in total lung capacity, vital capacity and  
10 functional residual capacity [10]. Loss of phrenic nerve function causes  
11 diaphragm weakness, which can lead to further complications. Despite the  
12 different presentations, most patients have speech impairment and airway  
13 clearance due to reduced bulbar muscle coordination [11].  
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15

16 The combination of inspiratory muscle weakness and reduced chest wall  
17 compliance limits the amount of volume needed for an effective cough.  
18 Inspiratory capacity represents the volume inspired until the end of the  
19 inspiratory phase of cough and is considered the most determining factor for  
20 peak cough flow (PCF) (i.e., affects length of expiratory muscle and efficiency  
21 of subsequent contraction). Also, adequate pressures to develop compressive  
22 forces and clear airway secretions are not achieved in the presence of glottic  
23 insufficiency. [12, 13, 14]  
24  
25

26 Impaired expiratory muscle contraction also decreases the ability to cough  
27 and clear secretions. Physiotherapists should assess and monitor vital  
28 capacity, MIP, SNIP, or peak expiratory cough flow of patients with ALS at  
29 least every three months [15, 16]. Physiotherapeutic interventions used in  
30 individuals with expiratory muscle weakness and secretion retention are lung  
31 volume recruitment, and airway clearance techniques with breath stacking, air  
32 stacking, and manually assisted coughing [17, 18, 19, 20].  
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35 In addition, inspiratory muscle training, lung volume recruitment training, and  
36 mechanical insufflation-exsufflation may also improve survival and should be  
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3 included in the overall management of ALS [16, 21].  
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5 This systematic review will investigate the effects of respiratory physiotherapy  
6 on lung function, cough efficacy and functional status of patients with ALS.  
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## 10 11 12 **REVIEW QUESTION** 13

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15 “What are the effects of respiratory physiotherapy on lung function, cough  
16 efficacy and functional status of patients with ALS?”  
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## 20 21 **METHODS AND ANALYSIS** 22

23  
24 The study will be conducted according to the Preferred reporting items for  
25 systematic reviews and meta-analysis guidelines (PRISMA-P) [22]. Searches  
26 in databases will be conducted from January 2021 to December 2022. The  
27 protocol for this review was submitted to the International Prospective  
28 Register of Systematic Reviews (PROSPERO), registration number  
29 CRD42021251842.  
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## 40 **Eligibility criteria** 41

42  
43 Randomised controlled trials (RCTs) performed with adult patients, all ages,  
44 of both genders and diagnosed with definite, probable, probable laboratory-  
45 supported, possible, or suspected ALS will be included if full-text or sufficient  
46 information about respiratory therapy and results are present. Non-  
47 randomized studies found during the search will be considered for the  
48 discussion section. Main steps of the search phase will be reported using a  
49 PRISMA flow diagram (Figure 1). Studies performed with patients with  
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3 neurodegenerative, cardiac, or respiratory diseases associated will be  
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5 excluded.  
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9 [Insert figure 1]  
10

## 11 **Types of interventions**

### 12 **Intervention**

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

### 30 **Comparators**

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

## 41 **Types of outcome measures**

### 42 **Primary outcomes**

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

### 45 **Secondary outcomes**

- 46 - 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](http://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. Analyses 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

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3 review. We will use a fixed-effect model to calculate pooled estimates and  
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5 95% confidence intervals (CIs). If significant heterogeneity exists, we will use  
6  
7 a random-effects model. We will use means and standard deviations (SD) to  
8  
9 calculate the mean difference (MD) and 95% CI for continuous variables. For  
10  
11 categorical outcomes, we will relate the numbers reporting an outcome to the  
12  
13 numbers at risk in each group to calculate a risk ratio (RR) and 95% CI. If  
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15 similar outcomes are reported on different scales, we will calculate the  
16  
17 standardised mean difference (SMD). If data to calculate RRs or MDs are not  
18  
19 given, we will utilise the most detailed numerical data available to calculate  
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21 the actual numbers or means and SD (for example, test statistics, p values).  
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### 28 **Grading the quality of evidence**

29  
30 The quality of evidence for all outcomes will be assessed using the GRADE  
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32 (Grading of Recommendations Assessment, Development and Evaluation)  
33  
34 [23] Working Group methodology through risk of bias, consistency, objectivity,  
35  
36 accuracy and reported bias. The certainty of evidence will be classified as  
37  
38 high, moderate, low or very low.  
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### 42 **Patient and public involvement**

43  
44 No patient involved.  
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### 48 **Discussion**

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51 Clinical trials with patients with ALS often present inconsistent results due to  
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53 the rapid progression of the disease and death. Despite knowledge regarding  
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55 respiratory physiotherapy techniques for patients with ALS, synthesizing and  
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57 highlighting effective therapies for increasing lung function may help clinical  
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3 practice; therefore, improving comfort. This systematic review will strengthen  
4 the level of evidence using information from randomized controlled trials and  
5 may be used as a guideline for the care of patients with ALS.  
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### 9 10 **Limitations**

11  
12 Possible limitations can be found, such as data heterogeneity, due to  
13 differences in intervention protocols and ALS diagnosis subtypes.  
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15 Impossibility of performing meta-analysis and possible methodological biases  
16 since the population studied is highly chronic and susceptible to  
17 exacerbations and deaths.  
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### 23 24 **Review status**

25  
26  
27 The study is in the data collection and analysis phase.  
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### 30 31 **Ethics and dissemination**

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33 Ethical approval is not required for this systematic review because data are  
34 already published and available publicly. This review intends to provide  
35 critically and summarized data to produce a practical guideline for respiratory  
36 care of patients with ALS.  
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39

### 40 41 **Author's contributions**

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

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*Figure Legend*

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

For peer review only

**Identification of studies via databases and registers**

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**Identification**

Records identified from:  
 Cochrane (n = )  
 EBSCO (n = )  
 Pubmed (n = )  
 PEDro (n = )  
 EMBASE (n = )

Records removed before screening:  
 Duplicate records removed by automation tools (n = )

**Screening**

Records screened (n = )

Records excluded (n = )

Reports sought for retrieval (n = )

Reports not retrieved (n = )

Reports assessed for eligibility (n = )

Reports excluded:  
 Study type (n = )  
 Study design (n = )  
 No results (n = )

**Included**

Studies included in the review (n = )

## 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

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## 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
<b>ADMINISTRATIVE INFORMATION</b>			
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	
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	Introduction 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
<b>METHODS</b>			
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 <sup>2</sup> , Kendall's $\tau$ )	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 where 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.**

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