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The Efficacy of the Proprioceptive Neuromuscular Facilitation (PNF) approach in stroke rehabilitation to improve basic activities of daily living and quality of life: a systematic review and meta-analysis protocol

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The Efficacy of the Proprioceptive Neuromuscular Facilitation (PNF) approach in stroke rehabilitation to improve basic activities of daily living and quality of life: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction: Proprioceptive neuromuscular facilitation (PNF) is an integrated approach although its efficacy has not yet been demonstrated in stroke survivors. The aim of this systematic review is to identify, assess and synthesize the potential benefits of PNF to improve the activities of daily living (ADL) and quality of life (QoL) in individuals with stroke.

Methods and analysis: A systematic hand search will be conducted in Medline, Embase, CENTRAL and PEDro. We will include randomized controlled trials or quasi-randomized of PNF intervention in stroke survivors until March 2016. Two review authors will independently select relevant studies and will extract data using the recommendations of the Cochrane Handbook for systematic reviews of interventions and the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). We will describe the results and conclusions of the included studies using the PEDro scale. If numeric data permit, we will carry out a meta-analysis.

Ethics and dissemination: No ethical consideration will be required. Results will be disseminating in a peer-review journal. This systematic review aims to examine the effects of PNF (neurophysiological approach) to clarify its efficacy to improve the ADL and QoL on the rehabilitation of stroke survivors.

Trial registration number: Prospero CRD42016039135

Keywords: Stroke, Proprioceptive neuromuscular facilitation, PNF, Kabat, Activities of daily living, Quality of life, Physiotherapy.

Strengths and limitations of this study

- To our knowledge this study is the first systematic review focalized in the proprioceptive neuromuscular facilitation (PNF) approach on stoke survivors.
- This systematic review has an open eligibility criteria's to clarify the efficacy of PNF method in different clinical situations for stroke patients.
- The electronic search was had language restriction to English, Spanish, Portuguese and French that could be limit the inclusion of studies.

INTRODUCTION

Stroke was the second most common cause of death worldwide in 2010 and the third cause of disability-adjusted life-years.[1-3]

Stroke survivors have dramatically reduced their activities of daily living (ADL)[4]and their quality of life (QoL) is significantly lower than general population.[5] 50% of individuals with stroke require support in their ADL[6] specially those related to basic self-maintenance task (domestic and community).[7] Further, some of these difficulties are related to motor functions impairments.[4] Moreover, the functionality is closely linked with QoL.[8] The conceptualization of QoL is a challenging endeavor and is being used in different ways, however only "satisfaction with life" is correct QoL conceptualization.[9] The principal factors that affect the QoL are related to functional status and disability, among others.[10]

Considering these aspects, it is important to focus stroke rehabilitation on the functional recovery related to movement considering that functional movement is the ability to produce and maintain balance between mobility and stability.[11] This proper coordination requires an effective proprioceptive communication between the muscles and joints. In order to improve the neuromuscular system's effectiveness in coordinating movement, there are different physiotherapy approaches amongst which is the proprioceptive neuromuscular facilitation (PNF).[12]

PNF approach exist since the late 1930s and '40s when a physician and neurologist named Herman Kabat and a physiotherapist Margaret Knott began using proprioceptive techniques on younger individuals with cerebral palsy and other neurological conditions. The main goal of this intervention method is to help patients to achieve their highest function level. PNF uses the body's proprioceptive system to facilitate or inhibit muscle contraction. The definition of PNF involves proprioceptive (having to do with any of the sensory receptors that give information concerning movement and position of the body); neuromuscular (involving the nerves and muscles) and facilitation (making easier).[13]

Recently, various systematic reviews have evaluated the efficacy of stroke rehabilitation interventions, including PNF[14-19] and a guideline.[20] However, none of them was specifically focused in PNF. Only a narrative review assessed PNF as the principal

topic.[21] Further, the most frequent objectives to assess the efficacy of this intervention method was motor function and mobility. In conclusion, no prior systematic reviews assessing the relationship between ADL and QoL were identified.
Eventually, it is necessary that therapist base their clinical decisions on the most reliable scientific evidence available.

OBJECTIVES

The purpose of this systematic review is: to examine the efficacy of proprioceptive neuromuscular facilitation (PNF) to improve the ADL and the QoL in individuals with stroke. Secondary specific aims are to determine the efficacy of the PNF in postural control, gait, upper limb function and in muscle strength.

METHODS:

This systematic review protocol was registered prospectively in Prospero (registration number: CRD42016039135) and will follow the recommendations of the Cochrane Handbook for systematic reviews of interventions[22] and will be reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[23]

Criteria for considering studies for this review

Type of studies

We will include all randomized controlled trials and quasi-randomized controlled trials.

Type of participants

We will include adult stroke participants (>18 years old) in the acute, subacute or chronic phase.

Type of interventions

We will include all trials which reported Proprioceptive Neuromuscular Facilitation (PNF) approach alone or in combination with another rehabilitation or medical intervention compared with a control group (conventional physiotherapy, another physiotherapy approach, no PNF, no treatment).

Type of outcomes measures

Primary outcomes:

i) Activities of daily living (ADL) evaluated mainly by Barthel Index (BI), Functional Independence Measures (FIM), modified Ranking Scale (mRS), Community Integration Questionnaire (CIQ).

ii) Quality of life (QoL) evaluated mainly by Medical Outcomes Study Short Form 36 (SF-36), Stroke Specific Quality of Life Scale (SS-QOL).

Secondary outcomes:

i) Postural control assessed mainly by Postural Assessment Scale for Stroke Patients (PASS) and Rivermead Mobility Index (RMI), Trunk Impairment Scale (TIS).

ii) Gait assessed mainly by Brunel Balance Assessment (BBA), Tinetti test, Functional Ambulation Category (FAC), Dynamic Gait Index (DGI), 6 Minute Walk Test (6MWT) or 10 Meter Walk Test (10MWT).

iii) Upper limb function assessed mainly by Wolf Motor Function (WMFT), Fugl-Meyer Assessment (FMA), Box and Block Test (BBT) or Motor Activity Log (MAL).

iv) Muscle strength assessed mainly by Oxford Scale, Hand-held Dynamometer/Grip Strength or Five Times Sit to Stand Test (FTSST).

Search methods for identification of studies

A systematic electronic search will be conducted in the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2016, Issue 3), MEDLINE (1964 to March 2016; via PubMed), EMBASE (1980 to March 2016; via Ovid) and PEDro (1999 to March 2016; via website). In addition, expert opinions' and the referent list of the selected studies and previous systematic reviews will be checked. Search strategy will involve two kinds of terms: "stroke" and "PNF" that will be combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format. Finally, language restrictions will be applied, only considering studies published in English, French, Spanish and Portuguese. This search

strategy is described in table 1.

Table 1 Medline (PubMed) search strategy

Stroke	1. "Cerebrovascular Disorders"[Mesh] OR stroke*[tiab] OR poststroke*[tiab] OR cerebral vascular OR accident*[tiab] OR cva*[tiab] OR brain injur*[ti] OR apoplex*[tiab] 2. "Brain"[Mesh] OR brain*[tiab] OR cerebr*[tiab] OR cerebell*[tiab] OR intracran*[tiab] OR intracerebral*[tiab] OR vertebrobasilar*[tiab] 3. "Blood vessels"[Mesh] OR blood vessel*[tiab] OR vascular*[tiab] OR "arteries"[Mesh] OR arter*[tiab] 4. "Intracranial Aneurysm"[Mesh] OR "Intracranial Hemorrhages"[Mesh] OR "Intracranial OR Hemorrhage, Hypertensive"[Mesh] OR "Hematoma, Subdural, Intracranial"[Mesh] OR "Subarachnoid Hemorrhage"[Mesh] OR "SAH"[tiab] 5. "Hemorrhage"[Mesh] OR hemorrhag*[tiab] OR haemorrhag*[tiab] OR "hematoma"[Mesh] OR hematoma*[tiab] OR haematoma*[tiab] OR bleed*[tiab] 6. "Intracranial Embolism and Thrombosis"[Mesh] OR "Intracranial Embolism"[Mesh] OR "Vasospasm, OR Intracranial"[Mesh] OR "Ischemic Attack, Transient"[Mesh] OR "TIA"[tiab] OR "Brain Ischemia"[Mesh] 7. "Ischemia"[Mesh] OR ischemi*[tiab] OR ischaemi*[tiab] OR thrombo*[tiab] OR "embolism"[Mesh] OR emboli*[tiab] OR oclus*[tiab] 8. "Disease"[Mesh] OR disease*[tiab] OR disorder*[tiab] OR infarc*[tiab] OR stenosi*[tiab] OR spasm*[tiab] OR accident*[tiab] 9. (#2 AND #7) OR #6 10. (((#2 OR subarachnoid*[tiab]) AND #5) OR #4) 11. #17 AND #23 AND #61 12. #1 OR #9 OR #10 OR #11
Proprioceptive neuromuscular facilitation (PNF)	13. Neuromuscular facilitation*[tiab] OR neuromuscular stimulation*[tiab] OR proprioceptive*[ti] OR "PNF"[tiab] OR autogenic inhibition*[tiab] OR reciprocal inhibition*[tiab] OR rhythmic stabilization*[tiab] OR repeat contraction*[tiab] OR repeated contraction*[tiab] OR hold relax*[tiab] OR antagonist contract*[tiab] OR slow reversal*[tiab] OR functional stretch reflex*[tiab] OR reflex excitability*[tiab] OR contract relax*[tiab] OR "kabat"[tiab]
Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing versión (2008 revision); PubMed format	14. Randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] 15. Animals [mh] NOT humans [mh] 16. #15 NOT #16
Final Search	17. #12 AND #13 AND #16

Data collection and analysis

Study Selection

Two review authors will independently screen all retrieved references and select studies that meet the selection criteria following these steps: (1) reading title and abstracts and then (2) by reading the full texts.

Data extraction and management

Two reviewers independently will extract data using a data extraction form, which will be designed, and tested prior to use. Disagreements will be resolved by discussion or, if necessary, referred to a third author.

The data extraction form will be based on the recommendations of the Cochrane handbook for systematic reviews of interventions[22] and will extract information from each selected study on demographic characteristics (e.g. age, gender, time since stroke, side of the paresis, unilateral or bilateral stroke, first ever or the recurrent stroke the etiologic and the localization of stroke lesions), study design, description of intervention in the experimental and control groups, risk of bias, outcomes measures and results. For a better data reporting, we will use the TIDieR (Template for intervention description and replication)[24] in the intervention section and the PEDro scale[25] to assess the risk of bias.

Assessment of the risk of bias in individual studies

Two review authors will independently evaluate the methodological quality from each selected study using the PEDro scale.[25] Disagreements will be resolved by involving a third author.

Measures of treatment effect

This review will express results from continuous outcomes with the mean difference (if the same scale is available) or standardized mean difference (if different scales were used) with 95% confidence intervals, and dichotomous outcomes with risk differences and 95% confidence intervals.[21]

Data synthesis

If a meta-analysis is possible, statistical analysis will be conducted by Revman 5.3. We will use fixed effects model to summarize the results of studies with non-significant heterogeneity; otherwise, we will use the random effects model. If there is great heterogeneity within the studies (I-squared >70%), which does not allow for a meta-analysis, a narrative synthesis of the available data will be conducted.[22]

Dealing with missing data

If data are missing, if possible, we will contact with the original authors to request the missing data, especially those necessary for the completion of the meta-analysis.[22]

Assessment of heterogeneity

Heterogeneity will be assessed using the I^2 statistic according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[21] Values greater than 50% will indicate the existence of substantial heterogeneity.[22]

Subgroup analysis and investigation of heterogeneity

We will consider the following subgroups: the etiology from the disease, type of stroke; stroke localization, stroke severity evaluated by the National institute of Health Stroke Scale (NIHSS) and modified Rankin Scale, thrombolysis and thrombectomy treatment, the chronicity of the disease. Finally, for the evaluation of the methodological heterogeneity will take in account the study design and the risk of bias of the studies included.[22]

Sensitivity analysis

We will perform a sensitivity analysis as follows: (a) random allocation, (b) concealed allocation, (c) methodological quality, (d) subjects blinding, (e) therapists blinding, (f) outcomes assessor blinding, and (g) intention to treat analysis and (h) drop outs.[22]

DISCUSSION

This systematic review will focus on the different techniques of Proprioceptive

Neuromuscular Facilitation (PNF) that are currently applied in stroke survivors to explore their influence in Activities of daily living (ADL) and Quality of life (QoL). PNF has been a very important part of therapeutic techniques for years. More recently, the focus on functional activities has allowed the techniques of PNF to become an integral part of this type of exercise programming. PNF can and should be incorporated into any functional training by stroke survivors.

FOOTNOTES

Acknowledgements: We would like to acknowledge the contribution of Blanquerna School of Science (Universitat Ramon Llull) and Iberoamerican Cochrane Center for their support to the first author.

Contributor ship statement: MS and XG designed and drafted the initial part of this study protocol. After that, all authors did substantial contributions to the design of the work; the analysis, and the interpretation of data for the work; and drafting the work and revising it critically for important intellectual content; and final approval of the version to be published; and all authors agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interest: The authors declare they have no competing interests.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	No
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	No
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	No
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	No
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	No
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	No
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	No
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Keywords: Stroke, Proprioceptive neuromuscular facilitation, PNF, Kabat, Activities of daily living, Quality of life, Physiotherapy.

Strengths and limitations of this study

- To our knowledge this study is the first systematic review focused in the proprioceptive neuromuscular facilitation (PNF) approach for stroke survivors.
- This systematic review has an open eligibility criteria to clarify the efficacy of the PNF method for different clinical situations in stroke patients.
- The electronic search will only include randomized controlled trials published in English, Spanish, French and Portuguese that could limit the inclusion of studies.

INTRODUCTION

Although age-standardized rates of stroke mortality have decreased worldwide in the past two decades, the total number of people who have a stroke every year, as well as stroke survivors, related deaths, and the overall global burden of stroke (DALYs lost) is increasing.[1]

Stroke survivors dramatically reduce their activities of daily living (ADL)[2] and their quality of life (QoL) is significantly lower than that of the general population.[3] 50% of individuals with stroke require support in their ADL[4] specially in those related to basic self-maintenance tasks (domestic and community).[5] Treatments are focused to recover maximal functions of stroke survivors at discharge, and hence may be an important factor to improve the functionality and Qol in stroke survivors.[6] The QoL construct has fluctuated over the years and at present has multiple conceptualizations, as a result, the clinical studies do not accurately define what QoL is and how it operates.[7 8] The current trend is that the conceptualization of QoL is classified over three different areas; QoL as a subjective well-being; QoL as achievements; and QoL as utility.[8] QoL as achievements refers to people's possessions, relationships and accomplishments, among others, using metrics defined by an outsider's point of view. In QoL as utility, achievements and statuses are judged in terms of societal norms and standards that quantify the value of a life.

Considering these aspects, it is important to focus stroke rehabilitation on the functional recovery related to movement considering that functional movement is the ability to produce and maintain balance between mobility and stability.[9] This proper coordination requires an effective proprioceptive communication between the muscles and joints. In order to improve the neuromuscular system's effectiveness in coordinating movement, there are different physiotherapy approaches amongst which is the proprioceptive neuromuscular facilitation (PNF).[10]

PNF approach has existed since the late 1930s and '40s when a physician and neurologist; Herman Kabat, and a physiotherapist; Margaret Knott, began using proprioceptive techniques on younger individuals with cerebral palsy and other neurological conditions. The main goal of this intervention method is to help patients to achieve their highest function level. PNF uses the body's proprioceptive system to

facilitate or inhibit muscle contraction. The definition of PNF involves proprioceptive (having to do with any of the sensory receptors that give information concerning movement and position of the body); neuromuscular (involving the nerves and muscles) and facilitation (making it easier).[11]

Recently, various systematic reviews have evaluated the efficacy of stroke rehabilitation interventions, including PNF[12-17] and a guideline.[18] However, none were specifically focused on PNF, with only a narrative review assessing PNF as the principal topic.[19] Furthermore, the most frequent objectives to assess the efficacy of this intervention method was motor function and mobility. It is necessary that therapists base their clinical decisions on the most reliable scientific evidence available, hence this systematic review aims to determine the efficacy of PNF techniques to improve the ADL and QoL in stroke survivors, by determining the efficacy of PNF techniques.

OBJECTIVES

The purpose of this systematic review is: to examine the efficacy of proprioceptive neuromuscular facilitation (PNF) to improve the ADL and the QoL in individuals with stroke. Secondary specific aims are to determine the efficacy of the PNF techniques in postural control, gait, upper limb function and in muscle strength.

METHODS:

This systematic review protocol was registered prospectively in Prospero (registration number: CRD42016039135) and will follow the recommendations of the Cochrane Handbook for systematic reviews of interventions[20] and will be reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[21]

Criteria for considering studies for this review

Type of studies

We will include all randomized controlled trials and quasi-randomized controlled trials.

Type of participants

We will include adult stroke participants (>18 years old) in the acute, subacute or chronic phase.

Type of interventions

We will include all trials which reported Proprioceptive Neuromuscular Facilitation (PNF) approach alone or in combination with another rehabilitation or medical intervention compared with a control group (conventional physiotherapy, another physiotherapy approach, no PNF, no treatment).

Type of outcomes measures

Primary outcomes:

i) Activities of daily living (ADL) evaluated mainly by Barthel Index (BI), Functional Independence Measures (FIM), modified Ranking Scale (mRS) and Community Integration Questionnaire (CIQ).

ii) Quality of life (QoL) evaluated mainly by Medical Outcomes Study Short Form 36 (SF-36) and Stroke Specific Quality of Life Scale (SS-QOL).

Secondary outcomes:

i) Postural control assessed mainly by Postural Assessment Scale for Stroke Patients (PASS), Rivermead Mobility Index (RMI) and the Trunk Impairment Scale (TIS).

ii) Gait assessed mainly by Brunel Balance Assessment (BBA), Tinetti test, Functional Ambulation Category (FAC), Dynamic Gait Index (DGI), 6 Minute Walk Test (6 MWT) or 10 Meter Walk Test (10 MWT).

iii) Upper limb function assessed mainly by Wolf Motor Function (WMFT), Fugl-Meyer Assessment (FMA), Box and Block Test (BBT) or Motor Activity Log (MAL).

iv) Muscle strength assessed mainly by Oxford Scale, Hand-held Dynamometer/Grip Strength or Five Times Sit to Stand Test (FTSST).

Search methods for identification of studies

A systematic electronic search will be conducted in the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library,

2017, Issue 3), MEDLINE (1964 to April 2017; via PubMed), EMBASE (1980 to April 2017; via Ovid) and PEDro (1999 to April 2017; via website). In addition, expert opinions' and the referent list of the selected studies and previous systematic reviews will be reviewed. The Search strategy will involve two kinds of terms: "stroke" and "PNF" that will be combined with the Cochrane Highly Sensitive Search Strategy for the identification of randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format. Finally, all studies published in English, Spanish, French, and Portuguese will be included. This search strategy is described in table 1.

Table 1 Medline (PubMed) search strategy

Stroke	1. "Cerebrovascular Disorders"[Mesh] OR stroke*[tiab] OR poststroke*[tiab] OR cerebral vascular OR accident*[tiab] OR cva*[tiab] OR brain injur*[ti] OR apoplex*[tiab] 2. "Brain"[Mesh] OR brain*[tiab] OR cerebr*[tiab] OR cerebell*[tiab] OR intracran*[tiab] OR intracerebral*[tiab] OR vertebrobasilar*[tiab] 3. "Blood vessels"[Mesh] OR blood vessel*[tiab] OR vascular*[tiab] OR "arteries"[Mesh] OR arter*[tiab] 4. "Intracranial Aneurysm"[Mesh] OR "Intracranial Hemorrhages"[Mesh] OR "Intracranial OR Hemorrhage, Hypertensive"[Mesh] OR "Hematoma, Subdural, Intracranial"[Mesh] OR "Subarachnoid Hemorrhage"[Mesh] OR "SAH"[tiab] 5. "Hemorrhage"[Mesh] OR hemorrhag*[tiab] OR haemorrhag*[tiab] OR "hematoma"[Mesh] OR hematoma*[tiab] OR haematoma*[tiab] OR bleed*[tiab] 6. "Intracranial Embolism and Thrombosis"[Mesh] OR "Intracranial Embolism"[Mesh] OR "Vasospasm, OR Intracranial"[Mesh] OR "Ischemic Attack, Transient"[Mesh] OR "TIA"[tiab] OR "Brain Ischemia"[Mesh] 7. "Ischemia"[Mesh] OR ischemi*[tiab] OR ischaemi*[tiab] OR thrombo*[tiab] OR "embolism"[Mesh] OR emboli*[tiab] OR oclus*[tiab] 8. "Disease"[Mesh] OR disease*[tiab] OR disorder*[tiab] OR infarc*[tiab] OR stenosi*[tiab] OR spasm*[tiab] OR accident*[tiab] 9. (#2 AND #7) OR #6 10. (((#2 OR subarachnoid*[tiab]) AND #5) OR #4) 11. #17 AND #23 AND #61 12. #1 OR #9 OR #10 OR #11
Proprioceptive neuromuscular facilitation (PNF)	13. Neuromuscular facilitation*[tiab] OR neuromuscular stimulation*[tiab] OR proprioceptive*[ti] OR "PNF"[tiab] OR autogenic inhibition*[tiab] OR reciprocal inhibition*[tiab] OR rhythmic stabilization*[tiab] OR repeat contraction*[tiab] OR repeated contraction*[tiab] OR hold relax*[tiab] OR antagonist contract*[tiab] OR slow reversal*[tiab] OR functional stretch

	reflex*[tiab] OR reflex excitability*[tiab] OR contract relax*[tiab] OR "kabat"[tiab]
Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing versión (2008 revision); PubMed format	14. Randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] 15. Animals [mh] NOT humans [mh] 16. #15 NOT #16
Final Search	17. #12 AND #13 AND #16

Data collection and analysis

Study Selection

Two reviewers will independently screen all retrieved references and select studies that meet the inclusion criteria following these steps: (1) reading title and abstracts and then (2) by reading the full-texts.

Data extraction and management

Two reviewers independently will extract data using a data extraction form, which will be designed, and tested prior to use. Disparities will be resolved by discussion or, if necessary, referred to a third reviewer.

The data extraction form will be based on the recommendations of the Cochrane handbook for systematic reviews of interventions[20] and will extract information from each selected study on demographic characteristics (e.g. age, gender, time since stroke, side of the paresis, unilateral or bilateral stroke, first ever or the recurrent stroke the etiologic and the localization of stroke lesions), study design, description of intervention conducted both in the experimental and control groups, risk of bias, outcomes measures and results. For better data reporting, we will use the TIDieR (Template for intervention description and replication)[22] in the intervention section and the PEDro scale[23] to assess the risk of bias.

Assessment of the risk of bias in individual studies

Two reviewers will independently evaluate the methodological quality from each selected study using the PEDro scale.[23] Disparities will be resolved by involving a third author.

Measures of treatment effect

Within this systematic review, results from continuous outcomes will be reported with the mean difference (if the same scale is available) or standardized mean difference (if different scales were used) with 95% confidence intervals, and dichotomous outcomes with risk differences and 95% confidence intervals.[19]

Data synthesis

If a meta-analysis is possible, statistical analysis will be conducted by Revman 5.3. We will use a fixed effects model to summarize the results of the studies with non-significant heterogeneity; otherwise, we will use the random effects model. If there is great heterogeneity within the studies (I-squared >70%), which does not allow the performance of a meta-analysis, a narrative synthesis of the available data will be conducted.[20]

Dealing with missing data

If data is unreported, when possible, we will contact the original authors to request the missing data, especially for those necessary for the completion of the meta-analysis.[20]

Assessment of heterogeneity

Heterogeneity will be assessed using the I^2 statistic according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[20] Values greater than 50% will indicate the existence of substantial heterogeneity.[20]

Subgroup analysis and investigation of heterogeneity

We will consider the following variables: the etiology of the disease, type of stroke; stroke localization, stroke severity evaluated by the National institute of Health Stroke Scale (NIHSS) and modified Rankin Scale, thrombolysis and thrombectomy treatment,

and the chronicity of the disease. Finally, for the evaluation of the methodological heterogeneity, will take the study design and the risk of bias of the studies included into account.[20]

Sensitivity analysis

We will perform a sensitivity analysis as follows: (a) random allocation, (b) concealed allocation, (c) methodological quality, (d) subjects blinding, (e) therapists blinding, (f) outcomes assessor blinding, and (g) intention to treat analysis and (h) drop outs.[20]

DISCUSSION

This systematic review will focus on the different techniques of Proprioceptive Neuromuscular Facilitation (PNF) that are currently applied in stroke survivors to explore their influence in Activities of daily living (ADL) and Quality of life (QoL). PNF has been a very important part of the therapeutic techniques for years. More recently, the focus on functional activities has allowed the techniques of PNF to become an integral part of this type of exercise programming. PNF can and should be incorporated into any functional training by stroke survivors.

FOOTNOTES

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Contributorship statement: Francesc Xavier Guiu-Tula (FXGT) conceived, designed and co-ordinated the protocol review. He registered the protocol review in the Prospero database, wrote the protocol review, provided a clinical perspective and commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review. Rosa Cabanas-Valdés (RCV) provided a clinical perspective, especially to the PNF method. She contributes to the outcome assessment and commented on drafts of the protocol review, and contributed to and approved the final

manuscript of the protocol review. Mercè Sitjà-Rabert (MSR) conceived and designed the review. She provided a methodological perspective and she wrote the manuscript and commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review. Gerard Urrútia (GU) provided a methodological perspective, commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review. Natàlia Gómara-Toldrà (NGT) provided a clinical perspective, especially to the assessment outcomes and quality of life construct. She wrote the manuscript and commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review.

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Competing interest: The authors declare not to have any competing interests.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	No
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	No
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	No
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	No
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	No
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	No
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	No
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

The Efficacy of the Proprioceptive Neuromuscular Facilitation (PNF) approach in stroke rehabilitation to improve basic activities of daily living and quality of life: a systematic review and meta-analysis protocol

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	Proprioceptive neuromuscular facilitation, PNF, Kabat, Activities of daily living, Quality of life, Stroke < NEUROLOGY

The Efficacy of the Proprioceptive Neuromuscular Facilitation (PNF) approach in stroke rehabilitation to improve basic activities of daily living and quality of life: a systematic review and meta-analysis protocol

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The Efficacy of the Proprioceptive Neuromuscular Facilitation (PNF) approach in stroke rehabilitation to improve basic activities of daily living and quality of life: a systematic review and meta-analysis protocol

ABSTRACT

Introduction: Proprioceptive neuromuscular facilitation (PNF) is a widely used rehabilitation concept although its efficacy has not yet been demonstrated in stroke survivors. The aim of this systematic review is to identify, assess and synthesize the potential benefits of PNF to improve the activities of daily living (ADL) and quality of life (QoL) in individuals with stroke.

Methods and analysis: A systematic electronic search will be conducted in Medline, Embase, CENTRAL and PEDro. We will include randomized controlled trials or quasi-randomized of PNF interventions in stroke survivors until April 2017. Two reviewers authors will independently select relevant studies and will extract data using the approach of the Cochrane Handbook for systematic reviews of interventions and the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). The methodological quality will be assessed by using the PEDro scale. Finally, the numeric data permitting, we will carry out a meta-analysis.

Ethics and dissemination: No ethical considerations will be required. Results will be disseminated in a peer-review journal. This systematic review aims to examine the effects of PNF (neurophysiological approach) in order to clarify its efficacy to improve the ADL and QoL in the rehabilitation process of stroke survivors.

Trial registration number: Prospero CRD42016039135

Keywords: Stroke, Proprioceptive neuromuscular facilitation, PNF, Kabat, Activities of daily living, Quality of life, Physiotherapy.

Strengths and limitations of this study

- To our knowledge this study is the first systematic review focused in the proprioceptive neuromuscular facilitation (PNF) approach for stroke survivors.
- This systematic review has an open eligibility criteria to clarify the efficacy of the PNF method for different clinical situations in stroke patients.
- The electronic search will only include randomized controlled and quasi-randomized controlled trials published in English, Spanish, French and Portuguese that could limit the inclusion of studies.

INTRODUCTION

Although age-standardized rates of stroke mortality have decreased worldwide in the past two decades, the total number of people who have a stroke every year, as well as stroke survivors, related deaths, and the overall global burden of stroke (DALYs lost) is increasing.[1] Motor function deficits due to stroke affect the patients' mobility, their limitation in daily life activities, their participation in society and their odds of returning to professional activities. All of these factors contribute to a low overall quality of life (QoL).[2]

The QoL construct has evolved over the years, with multiple conceptualizations. As a result, the majority of the clinical studies do not accurately define the QoL and how it operationalized.[3,4] Dijkers separated QoL into three categories: (1) QoL as subjective well-being (SWB), (2) QoL as achievements, and (3) QoL as utility. QoL as SWB have been defined as the sum total of the cognitive and emotional reactions that people experience when they compare what they have and do in life with their aspirations, needs, and other expectations. QoL as achievements refers to people's possessions, relationships and accomplishments, among others, using metrics defined by an outsider's point of view. In QoL as utility, achievements and statuses are judged in terms of societal norms and standards that quantify the value of a life.[4] In the field of medical rehabilitation, QoL measurement commonly involved health status or was qualified by the term "health-related". Health related quality of life (HRQoL) is defined by the value assigned to duration of life as modified by impairment, functional state, perception and social factors that are influenced by the disease, injury, treatment or policy.[5]

Successful rehabilitation effectively addresses the components of the International Classification of Functioning (ICF) (impairment, activity limitations and participation restrictions, contextual and personal factors) with a goal of a satisfactory QoL as perceived by the individual. The relationship between the three domains of the ICF is clear: impairments have an impact on activities and activities have an impact on participation. Functionality and activities of daily living (ADL) take a specific role influencing positively QoL in stroke survivors. During the recovery process according to the disability grade, it is important to impact on that variables at any time through the rehabilitation treatment, taking into account that are variable that change over the time.[6] Much of the focus of stroke rehabilitation is on the recovery of impaired movement and

the associated functions. There seems to be a direct relation between motor impairment and function; for example, independence in walking (function) has been correlated with lower-limb strength (impairment).[7] In order to improve the neuromuscular system's effectiveness in coordinating movement and function, there are different physical rehabilitation approaches used for enhancing recovery in post stroke patients, but no one was more (or less) effective than any other approach in improving independence in ADL or motor function.[8] In rehabilitation practice is widely used the proprioceptive neuromuscular facilitation (PNF).[9]

PNF approach has existed since the late 1930s and '40s when a physician and neurologist Herman Kabat, and a physiotherapist Margaret Knott, began using proprioceptive techniques on younger individuals with cerebral palsy and other neurological conditions. The main goal of this intervention method is to help patients to achieve their highest function level. PNF uses the body's proprioceptive system to facilitate or inhibit muscle contraction. The definition of PNF involves proprioceptive (having to do with any of the sensory receptors that give information concerning movement and position of the body); neuromuscular (involving the nerves and muscles) and facilitation (making it easier).[10]

Recently, various systematic reviews have evaluated the efficacy of stroke rehabilitation interventions, including PNF[11-15] and a guideline.[16] However, none were specifically focused on PNF, with only a narrative review assessing PNF as the principal topic.[9] Furthermore, the most frequent objectives to assess the efficacy of this intervention method was motor function and mobility. It is necessary that therapists base their clinical decisions on the most reliable scientific evidence available; hence, this systematic review aims to determine the efficacy of PNF techniques to improve the ADL and QoL in stroke survivors, by determining the efficacy of PNF techniques.

OBJECTIVES

The purpose of this systematic review is to examine the efficacy of proprioceptive neuromuscular facilitation (PNF) to improve the ADL and the QoL in individuals with stroke. Secondary specific aims are to determine the efficacy of the PNF techniques in postural control, gait, upper limb function and in muscle strength.

METHODS:

This systematic review protocol was registered prospectively in Prospero (registration number: CRD42016039135) and will follow the recommendations of the Cochrane Handbook for systematic reviews of interventions[17] and will be reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[18]

Criteria for considering studies for this review

Type of studies

We will include all randomized controlled trials and quasi-randomized controlled trials.

Type of participants

We will include adult stroke participants (>18 years old) in the acute, subacute or chronic phase.

Type of interventions

We will include all trials which reported Proprioceptive Neuromuscular Facilitation (PNF) approach alone or in combination with another rehabilitation or medical intervention compared with a control group (conventional physiotherapy, another physiotherapy approach, no PNF, no treatment).

Type of outcomes measures

Primary outcomes:

i) Activities of daily living (ADL) evaluated mainly by Barthel Index (BI), Functional Independence Measures (FIM), modified Ranking Scale (mRS) and Community Integration Questionnaire (CIQ).

ii) Quality of life (QoL) evaluated mainly by Medical Outcomes Study Short Form 36 (SF-36) and Stroke Specific Quality of Life Scale (SS-QOL).

Secondary outcomes:

i) Postural control assessed mainly by Postural Assessment Scale for Stroke Patients (PASS), Rivermead Mobility Index (RMI) and the Trunk Impairment Scale (TIS).

ii) Gait assessed mainly by Brunel Balance Assessment (BBA), Tinetti test, Functional Ambulation Category (FAC), Dynamic Gait Index (DGI), 6 Minute Walk Test (6 MWT) or 10 Meter Walk Test (10 MWT).

iii) Upper limb function assessed mainly by Wolf Motor Function (WMFT), Fugl-Meyer Assessment (FMA), Box and Block Test (BBT) or Motor Activity Log (MAL).

iv) Muscle strength assessed mainly by Oxford Scale, Hand-held Dynamometer/Grip Strength or Five Times Sit to Stand Test (FTSST).

Search methods for identification of studies

A systematic electronic search will be conducted in the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2017, Issue 3), MEDLINE (1964 to April 2017; via PubMed), EMBASE (1980 to April 2017; via Ovid) and PEDro (1999 to April 2017; via website). In addition, expert opinions' and the referent list of the selected studies and previous systematic reviews will be reviewed. The Search strategy will involve two kinds of terms: "stroke" and "PNF" that will be combined with the Cochrane Highly Sensitive Search Strategy for the identification of randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format. Finally, all studies published in English, Spanish, French, and Portuguese will be included. This search strategy is described in table 1.

Table 1 Medline (PubMed) search strategy

Stroke	1. "Cerebrovascular Disorders"[Mesh] OR stroke*[tiab] OR poststroke*[tiab] OR cerebral vascular OR accident*[tiab] OR cva*[tiab] OR brain injur*[ti] OR apoplex*[tiab] 2. "Brain"[Mesh] OR brain*[tiab] OR cerebr*[tiab] OR cerebell*[tiab] OR intracran*[tiab] OR intracerebral*[tiab] OR vertebrobasilar*[tiab] 3. "Blood vessels"[Mesh] OR blood vessel*[tiab] OR vascular*[tiab] OR "arteries"[Mesh] OR arter*[tiab] 4. "Intracranial Aneurysm"[Mesh] OR "Intracranial Hemorrhages"[Mesh] OR "Intracranial OR Hemorrhage, Hypertensive"[Mesh] OR "Hematoma, Subdural, Intracranial"[Mesh] OR "Subarachnoid Hemorrhage"[Mesh] OR "SAH"[tiab] 5. "Hemorrhage"[Mesh] OR hemorrhag*[tiab] OR haemorrhag*[tiab] OR "hematoma"[Mesh] OR hematoma*[tiab] OR haematoma*[tiab] OR bleed*[tiab] 6. "Intracranial Embolism and Thrombosis"[Mesh] OR "Intracranial Embolism"[Mesh] OR "Vasospasm, OR Intracranial"[Mesh] OR "Ischemic Attack, Transient"[Mesh] OR "TIA"[tiab] OR "Brain Ischemia"[Mesh] 7. "Ischemia"[Mesh] OR ischemi*[tiab] OR ischaemi*[tiab] OR thrombo*[tiab] OR "embolism"[Mesh] OR emboli*[tiab] OR oclus*[tiab] 8. "Disease"[Mesh] OR disease*[tiab] OR disorder*[tiab] OR infarc*[tiab] OR stenosi*[tiab] OR spasm*[tiab] OR accident*[tiab] 9. (#2 AND #7) OR #6 10. (((#2 OR subarachnoid*[tiab]) AND #5) OR #4) 11. #17 AND #23 AND #61 12. #1 OR #9 OR #10 OR #11
Proprioceptive neuromuscular facilitation (PNF)	13. Neuromuscular facilitation*[tiab] OR neuromuscular stimulation*[tiab] OR proprioceptive*[ti] OR "PNF"[tiab] OR autogenic inhibition*[tiab] OR reciprocal inhibition*[tiab] OR rhythmic stabilization*[tiab] OR repeat contraction*[tiab] OR repeated contraction*[tiab] OR hold relax*[tiab] OR antagonist contract*[tiab] OR slow reversal*[tiab] OR functional stretch reflex*[tiab] OR reflex excitability*[tiab] OR contract relax*[tiab] OR "kabat"[tiab]
Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing versión (2008 revision); PubMed format	14. Randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] 15. Animals [mh] NOT humans [mh] 16. #15 NOT #16
Final Search	17. #12 AND #13 AND #16

Data collection and analysis

Study Selection

Two reviewers will independently screen all retrieved references and select studies that meet the inclusion criteria following these steps: (1) reading title and abstracts and then (2) by reading the full-texts.

Data extraction and management

Two reviewers independently will extract data using a data extraction form, which will be designed and tested prior to use. Disparities will be resolved by discussion or if necessary, referred to a third reviewer. The data extraction form will be based on the recommendations of the Cochrane handbook for systematic reviews of interventions[17] and will be extracted information from each selected study on demographic characteristics (example; age, gender, time since stroke, side of the paresis, unilateral or bilateral stroke, first ever or the recurrent stroke the etiologic and the localization of stroke lesions), study design, description of intervention conducted both in the experimental and control groups, risk of bias, outcomes measures and results. For better data reporting, we will use the TIDieR (Template for intervention description and replication)[19] in the intervention section and the PEDro scale[20] to assess the risk of bias.

Assessment of the risk of bias in individual studies

Two reviewers will independently evaluate the methodological quality from each selected study using the PEDro scale.[20] Disparities will be resolved by involving a third author.

Measures of treatment effect

Within this systematic review, results from continuous outcomes will be reported with the mean difference (if the same scale is available) or standardized mean difference (if different scales were used) with 95% confidence intervals, and dichotomous outcomes with risk differences and 95% confidence intervals.[17]

Data synthesis

If a meta-analysis is possible, statistical analysis will be conducted by Revman 5.3. We

will use a fixed effects model to summarize the results of the studies with non-significant heterogeneity; otherwise, we will use the random effects model. If there is great heterogeneity within the studies (I-squared >70%), which does not allow the performance of a meta-analysis, a narrative synthesis of the available data will be conducted.[17]

Dealing with missing data

If data is unreported, when possible, we will contact the original authors to request the missing data, especially for those necessary for the completion of the meta-analysis.[17]

Assessment of heterogeneity

Heterogeneity will be assessed using the I^2 statistic according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[17] Values greater than 50% will indicate the existence of substantial heterogeneity.[17]

Subgroup analysis and investigation of heterogeneity

We will consider the following variables: the etiology of the disease, type of stroke; stroke localization, stroke severity evaluated by the National institute of Health Stroke Scale (NIHSS) and modified Rankin Scale, thrombolysis and thrombectomy treatment, and the chronicity of the disease. Finally, for the evaluation of the methodological heterogeneity, will take the study design and the risk of bias of the studies included into account.[17]

Sensitivity analysis

We will perform a sensitivity analysis as follows: (a) random allocation, (b) concealed allocation, (c) methodological quality, (d) subjects blinding, (e) therapists blinding, (f) outcomes assessor blinding, and (g) intention to treat analysis and (h) drop outs.[17]

DISCUSSION

This systematic review will focus on the different techniques of Proprioceptive Neuromuscular Facilitation (PNF) that are currently applied in stroke survivors to

explore their influence in Activities of daily living (ADL) and Quality of life (QoL). PNF has been a very important part of the therapeutic techniques for years. More recently, the focus on functional activities has allowed the techniques of PNF to become an integral part of this type of exercise programming. PNF can and should be incorporated into any functional training by stroke survivors.

FOOTNOTES

Acknowledgements: We would like to acknowledge the contribution of Blanquerna School of Health Science (Ramon Llull University) and Iberoamerican Cochrane Center to serve their installations and services to the first author. We would like to acknowledge the contribution of Montse León (ML) and Gary Gibson (GG) for his assistance and help in the editing process of the manuscript.

Contributor ship statement: Francesc Xavier Guiu Tula (FXGT) conceived, designed and co-ordinated the protocol review. He registered the protocol review in the Prospero database, wrote the protocol review, provided a clinical perspective and commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review. Rosa Cabanas Valdés (RCV) provided a clinical perspective, especially to the PNF method. She contributes to the outcome assessment and commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review. Mercè Sitjà-Rabert (MSR) conceived and designed the review. She provided a methodological perspective and she wrote the manuscript and commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review. Gerard Urrútia (GU) provided a methodological perspective, commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review. Natàlia Gómara Toldrà (NGT) provided a clinical perspective, especially to the assessment outcomes and quality of life construct. She wrote the manuscript and commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review.

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Competing interest: The authors declare not to have any competing interests.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	No
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	No
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	No
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	No
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	No
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	No
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	No
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

The Efficacy of the Proprioceptive Neuromuscular Facilitation (PNF) approach in stroke rehabilitation to improve basic activities of daily living and quality of life: a systematic review and meta-analysis protocol

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	Proprioceptive neuromuscular facilitation, PNF, Kabat, Activities of daily living, Quality of life, Stroke < NEUROLOGY

The Efficacy of the Proprioceptive Neuromuscular Facilitation (PNF) approach in stroke rehabilitation to improve basic activities of daily living and quality of life: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction: Proprioceptive neuromuscular facilitation (PNF) is a widely used rehabilitation concept although its efficacy has not yet been demonstrated in stroke survivors. The aim of this systematic review is to identify, assess and synthesize the potential benefits of PNF to improve the activities of daily living (ADL) and quality of life (QoL) in individuals with stroke.

Methods and analysis: A systematic electronic search will be conducted in Medline, Embase, CENTRAL and PEDro. We will include randomized controlled trials or quasi-randomized of PNF interventions in stroke survivors until April 2017. Two reviewers authors will independently select relevant studies and will extract data using the approach of the Cochrane Handbook for systematic reviews of interventions and the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). The methodological quality will be assessed by using the PEDro scale. Finally, the numeric data permitting, we will carry out a meta-analysis.

Ethics and dissemination: No ethical considerations will be required. Results will be disseminated in a peer-review journal. This systematic review aims to examine the effects of PNF (neurophysiological approach) in order to clarify its efficacy to improve the ADL and QoL in the rehabilitation process of stroke survivors.

Trial registration number: Prospero CRD42016039135

Keywords: Stroke, Proprioceptive neuromuscular facilitation, PNF, Kabat, Activities of daily living, Quality of life, Physiotherapy.

Strengths and limitations of this study

- To our knowledge this study is the first systematic review focused in the proprioceptive neuromuscular facilitation (PNF) approach for stroke survivors.
- This systematic review has an open eligibility criteria to clarify the efficacy of the PNF method for different clinical situations in stroke patients.
- The electronic search will only include randomized controlled and quasi-randomized controlled trials published in English, Spanish, French and Portuguese that could limit the inclusion of studies.

INTRODUCTION

Although age-standardized rates of stroke mortality have decreased worldwide in the past two decades, the total number of people who have a stroke every year, as well as stroke survivors, related deaths, and the overall global burden of stroke (DALYs lost) is increasing.[1] Motor function deficits due to stroke often affect the patients' mobility, their limitation in daily life activities, their participation in society and their odds of returning to professional activities. Motor function among others factors (as social or personal factors) could contribute to a low overall quality of life (QoL).[2]

A number of conceptualizations have been used through the years to describe QoL in stroke survivors.[3-5] The lack of an agreed definition about QoL causes that most of the QoL outcomes were assessed with standarised questionaries. However, they do not reflect the important domains of the patients QoL and sometimes scores may be difficult to interpret.[5]

Dijkers[4] separated QoL term into three categories: (1) QoL as subjective well-being (SWB), (2) QoL as achievements, and (3) QoL as utility. QoL as SWB has been defined as the sum total of the cognitive and emotional reactions that people experience when they compare what they have and do in life with their aspirations, needs, and other expectations. QoL as achievements refers to people's possessions, relationships and accomplishments, among others, using metrics defined by an outsider's point of view. In the field of medical rehabilitation, QoL measurement commonly involved health status or was qualified by the term "health-related". Health-related QoL (HRQoL) is a major subcategory of this type of QoL: in measures developed to operationalize HRQoL, the statuses are limited very much to those traditionally under the purview of the medical establishment, including physical and mental health and symptoms. HRQoL is defined by the value assigned to duration of life as modified by impairment, functional state, perception and social factors that are influenced by the disease, injury, treatment or policy.[6] According to Dijkers,[4] some researchers, basing themselves on the World Health Organization's (WHO's) encompassing definition of health, may add to this mix social health indicators such as interactions with others and social role functioning. Finally, in QoL as utility, achievements and statuses are judged in terms of societal norms and standards that quantify the value of a life.

Successful rehabilitation effectively addresses the components of the International Classification of Functioning (ICF) (impairment, activity limitations and participation restrictions, contextual and personal factors) with a goal of a satisfactory QoL as perceived by the individual. The relationship between the three domains of the ICF is clear: impairments impact activities and activities have an impact on participation. Functionality and activities of daily living (ADL) take a specific role influencing positively QoL in stroke survivors. During the recovery process according to the disability grade, it is important to impact on that variables at any time through the rehabilitation treatment, taking into account that are variable that change over the time.[7] Much of the focus of stroke rehabilitation is on the recovery of impaired movement and the associated functions. There seems to be a direct relation between motor impairment and function; for example, independence in walking (function) has been correlated with lower-limb strength (impairment).[8] In order to improve the neuromuscular system's effectiveness in coordinating movement and function, there are different physical rehabilitation approaches used for enhancing recovery in post stroke patients, but no one was more (or less) effective than any other method in improving independence in ADL or motor function.[9] In rehabilitation practice is widely used the proprioceptive neuromuscular facilitation (PNF).[10]

PNF approach has existed since the late 1930s and '40s when a physician and neurologist; Herman Kabat, and a physiotherapist; Margaret Knott, began using proprioceptive techniques on younger individuals with cerebral palsy and other neurological conditions. The main goal of this intervention method is to help patients to achieve their highest function level. PNF uses the body's proprioceptive system to facilitate or inhibit muscle contraction. The definition of PNF involves proprioceptive (having to do with any of the sensory receptors that give information concerning movement and position of the body); neuromuscular (involving the nerves and muscles) and facilitation (making it easier).[11]

Recently, various systematic reviews have evaluated the efficacy of stroke rehabilitation interventions, including PNF[12-17] and a guideline.[18] However, none were specifically focused on PNF, with only a narrative review assessing PNF as the principal topic.[10] Furthermore, the most frequent objectives to assess the efficacy of this intervention method was motor function and mobility. It is necessary that therapists base their

clinical decisions on the most reliable scientific evidence available; hence this systematic review aims to determine the efficacy of PNF techniques to improve the ADL and QoL in stroke survivors, by determining the efficacy of PNF techniques.

OBJECTIVES

The purpose of this systematic review is: to examine the efficacy of proprioceptive neuromuscular facilitation (PNF) to improve the ADL and the QoL in individuals with stroke. Secondary specific aims are to determine the efficacy of the PNF techniques in postural control, gait, upper limb function and in muscle strength.

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This systematic review protocol was registered prospectively in Prospero (registration number: CRD42016039135) and will follow the recommendations of the Cochrane Handbook for systematic reviews of interventions[19] and will be reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[20]

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A systematic electronic search will be conducted in the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2017, Issue 3), MEDLINE (1964 to April 2017; via PubMed), EMBASE (1980 to April 2017; via Ovid) and PEDro (1999 to April 2017; via website). In addition, expert opinions' and the referent list of the selected studies and previous systematic reviews will be reviewed. The Search strategy will involve two kinds of terms: "stroke" and "PNF" that will be combined with the Cochrane Highly Sensitive Search Strategy for the identification of randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format. Finally, all studies published in English, Spanish, French, and Portuguese will be included. This search strategy is described in table 1.

Table 1 Medline (PubMed) search strategy

Stroke	1. "Cerebrovascular Disorders"[Mesh] OR stroke*[tiab] OR poststroke*[tiab] OR cerebral vascular OR accident*[tiab] OR cva*[tiab] OR brain injur*[ti] OR apoplex*[tiab] 2. "Brain"[Mesh] OR brain*[tiab] OR cerebr*[tiab] OR cerebell*[tiab] OR intracran*[tiab] OR intracerebral*[tiab] OR vertebrobasilar*[tiab] 3. "Blood vessels"[Mesh] OR blood vessel*[tiab] OR vascular*[tiab] OR "arteries"[Mesh] OR arter*[tiab] 4. "Intracranial Aneurysm"[Mesh] OR "Intracranial Hemorrhages"[Mesh] OR "Intracranial OR Hemorrhage, Hypertensive"[Mesh] OR "Hematoma, Subdural, Intracranial"[Mesh] OR "Subarachnoid Hemorrhage"[Mesh] OR "SAH"[tiab] 5. "Hemorrhage"[Mesh] OR hemorrhag*[tiab] OR haemorrhag*[tiab] OR "hematoma"[Mesh] OR hematoma*[tiab] OR haematoma*[tiab] OR bleed*[tiab] 6. "Intracranial Embolism and Thrombosis"[Mesh] OR "Intracranial Embolism"[Mesh] OR "Vasospasm, OR Intracranial"[Mesh] OR "Ischemic Attack, Transient"[Mesh] OR "TIA"[tiab] OR "Brain Ischemia"[Mesh] 7. "Ischemia"[Mesh] OR ischemi*[tiab] OR ischaemi*[tiab] OR thrombo*[tiab] OR "embolism"[Mesh] OR emboli*[tiab] OR oclus*[tiab] 8. "Disease"[Mesh] OR disease*[tiab] OR disorder*[tiab] OR infarc*[tiab] OR stenosi*[tiab] OR spasm*[tiab] OR accident*[tiab] 9. (#2 AND #7) OR #6 10. (((#2 OR subarachnoid*[tiab]) AND #5) OR #4) 11. #17 AND #23 AND #61 12. #1 OR #9 OR #10 OR #11
Proprioceptive neuromuscular facilitation (PNF)	13. Neuromuscular facilitation*[tiab] OR neuromuscular stimulation*[tiab] OR proprioceptive*[ti] OR "PNF"[tiab] OR autogenic inhibition*[tiab] OR reciprocal inhibition*[tiab] OR rhythmic stabilization*[tiab] OR repeat contraction*[tiab] OR repeated contraction*[tiab] OR hold relax*[tiab] OR antagonist contract*[tiab] OR slow reversal*[tiab] OR functional stretch reflex*[tiab] OR reflex excitability*[tiab] OR contract relax*[tiab] OR "kabat"[tiab]
Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing versión (2008 revision); PubMed format	14. Randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] 15. Animals [mh] NOT humans [mh] 16. #15 NOT #16
Final Search	17. #12 AND #13 AND #16

Data collection and analysis

Study Selection

Two reviewers will independently screen all retrieved references and select studies that meet the inclusion criteria following these steps: (1) reading title and abstracts and then (2) by reading the full-texts.

Data extraction and management

Two reviewers independently will extract data using a data extraction form, which will be designed, and tested prior to use. Disparities will be resolved by discussion or, if necessary, referred to a third reviewer.

The data extraction form will be based on the recommendations of the Cochrane handbook for systematic reviews of interventions[19] and will extract information from each selected study on demographic characteristics (e.g. age, gender, time since stroke, side of the paresis, unilateral or bilateral stroke, first ever or the recurrent stroke the etiologic and the localization of stroke lesions), study design, description of intervention conducted both in the experimental and control groups, risk of bias, outcomes measures and results. For better data reporting, we will use the TIDieR (Template for intervention description and replication)[21] in the intervention section and the PEDro scale[22] to assess the risk of bias.

Assessment of the risk of bias in individual studies

Two reviewers will independently evaluate the methodological quality from each selected study using the PEDro scale.[22] Disparities will be resolved by involving a third author.

Measures of treatment effect

Within this systematic review, results from continuous outcomes will be reported with the mean difference (if the same scale is available) or standardized mean difference (if different scales were used) with 95% confidence intervals, and dichotomous outcomes with risk differences and 95% confidence intervals.[19]

Data synthesis

If a meta-analysis is possible, statistical analysis will be conducted by Revman 5.3. We

will use a fixed effects model to summarize the results of the studies with non-significant heterogeneity; otherwise, we will use the random effects model. If there is great heterogeneity within the studies (I-squared >70%), which does not allow the performance of a meta-analysis, a narrative synthesis of the available data will be conducted.[19]

Dealing with missing data

If data is unreported, when possible, we will contact the original authors to request the missing data, especially for those necessary for the completion of the meta-analysis.[19]

Assessment of heterogeneity

Heterogeneity will be assessed using the I^2 statistic according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[19] Values greater than 50% will indicate the existence of substantial heterogeneity.[19]

Subgroup analysis and investigation of heterogeneity

We will consider the following variables: the etiology of the disease, type of stroke; stroke localization, stroke severity evaluated by the National institute of Health Stroke Scale (NIHSS) and modified Rankin Scale, thrombolysis and thrombectomy treatment, and the chronicity of the disease. Finally, the evaluation of the methodological heterogeneity, will take the study design and the risk of bias of the studies included into account.[19]

Sensitivity analysis

We will perform a sensitivity analysis as follows: (a) random allocation, (b) concealed allocation, (c) methodological quality, (d) subjects blinding, (e) therapists blinding, (f) outcomes assessor blinding, and (g) intention to treat analysis and (h) drop outs.[19]

ETHICS AND DISSEMINATION

No ethical statement will be required for this review and meta-analysis. Results of this research will be published. These results will contribute to improve the therapeutic

strategy of patients with stroke.

DISCUSSION

This systematic review will focus on the different techniques of Proprioceptive Neuromuscular Facilitation (PNF) that are currently applied in stroke survivors to explore their influence in Activities of daily living (ADL) and Quality of life (QoL). PNF has been a very important part of the therapeutic techniques for years. More recently, the focus on functional activities has allowed the techniques of PNF to become an integral part of this type of exercise programming. PNF can and should be incorporated into any functional training by stroke survivors.

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Authors' contributions: Francesc Xavier Guiu Tula (FXGT) conceived, designed and co-ordinated the protocol review. He registered the protocol review in the Prospero database, wrote the protocol review, provided a clinical perspective and commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review. Rosa Cabanas Valdés (RCV) provided a clinical perspective, especially to the PNF method. She contributes to the outcome assessment and commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review. Mercè Sitjà-Rabert (MSR) conceived and designed the review. She provided a methodological perspective and she wrote the manuscript and commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review. Gerard Urrútia (GU) provided a methodological perspective, commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review. Natàlia Gómara Toldrà (NGT) provided a clinical perspective, especially to the assessment outcomes and quality of life

construct. She wrote the manuscript and commented on drafts of the protocol review, and contributed to and approved the final manuscript of the protocol review.

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Competing interest: The authors declare not to have any competing interests.

This protocol study has been presented at the 2º Congress on NeuroRehabilitation and Neural Repair from 22 to 24 May 2017 in Maastricht, the Netharlands.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	No
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	No
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	No
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	No
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	No
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	No
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	No
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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