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THE INFLUENCE OF ALLOCATION CONCEALMENT AND INTENTION-TO-TREAT ANALYSIS ON TREATMENT EFFECTS OF PHYSICAL THERAPY INTERVENTIONS IN LOW BACK PAIN RANDOMIZED CONTROLLED TRIALS: A PROTOCOL OF A META-EPIDEMIOLOGICAL STUDY

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THE INFLUENCE OF ALLOCATION CONCEALMENT AND INTENTION-TO-TREAT ANALYSIS ON TREATMENT EFFECTS OF PHYSICAL THERAPY INTERVENTIONS IN LOW BACK PAIN RANDOMIZED CONTROLLED TRIALS: A PROTOCOL OF A META-EPIDEMIOLOGICAL STUDY

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AUTHORS' CONTRIBUTIONS

MOA, BTS and LOPC conceived and designed the study. CM contributed to the development of the protocol. All of the authors assisted in the final protocol and agreed to its final approval before submission.

COMPETING INTEREST

None

ABSTRACT

Introduction: The presence of methodological bias, such as inadequate allocation concealment and lack of intention-to-treat analysis may overestimate the treatment effects from randomized controlled trials. Meta-epidemiological studies have been performed in a large number of health-care areas. However, there are no studies investigating these issues in physical therapy interventions for patients with low back pain. The aim of this study is to investigate the influence of allocation concealment and the use of intention-to-treat analysis on estimates of the treatment effects of physical therapy interventions in low back pain clinical trials from meta-analyses.

Methods and analysis: A search on PubMed, Embase, Cochrane Database of Systematic Reviews and PEDro databases will be performed. We will include all meta-analyses of randomized controlled trials that compared physical therapy interventions in patients with low back pain compared with placebo or no intervention, and have pain intensity or disability as the primary outcomes. Information about selection (allocation concealment) and attrition bias (intention-to-treat analysis) will be extracted from the PEDro Database. Information about bibliographic data, study characteristics, participants' characteristics and study results will be extracted from each systematic review. A random effect model of meta-analyses will be used to pool the effect sizes. Finally, a meta-regression will be performed to assess the association between methodological features (allocation concealment and intention to treat analysis) and effect sizes. The dependent variable will be the effect size (the mean between-group differences) for the primary outcomes (pain or disability), while the independent variables will be the methodological features of interest (allocation concealment and intention-to-treat analysis).

Ethics and dissemination: No ethical approval required for this study. The study findings will be published in a peer-reviewed journal and presented at national/international conferences.

Registration number: PROSPERO (CRD42016052347).

Keywords: Epidemiologic Research Design; Low Back Pain; Physical Therapy Modalities

Strengths and limitations of this study

- This protocol was performed following the Preferred Reporting Items for Systematic review and Meta-Analyses Protocols (PRISMA - P) guidelines.
- This study will be the first one to evaluate the association between methodological characteristics and the treatment effects of physical therapy interventions in low back pain trials.
- The results from this meta-epidemiological study are likely to bring new insights to the physical therapy scientific community by informing issues that need to be considered in randomized trials.

INTRODUCTION

Systematic reviews and meta-analyses of randomized controlled trials are considered the 'gold standard' to evaluate the efficacy and effectiveness of healthcare interventions.[1,2] Despite systematic reviews and meta-analyses providing the best available evidence to support clinical decision-making and to promote changes in health policies, they are not free of bias.[3,4] The presence of potential biases in clinical trials, such as inadequate allocation concealment (selection bias) or lack of intention-to-treat analysis (attrition bias) may overestimate the effect size of the interventions[5-8]. These types of bias can directly influence the results from meta-analyses, leading to inaccurate conclusions, misleading clinicians and researchers.[9]

Meta-epidemiological studies usually aim to understand the impact of study characteristics (i.e., methodological quality, study design) in randomized clinical trials (RCTs), investigating the association between specific these study characteristics and the intervention effect estimates from collections of meta-analyses.[10,11] A collection of meta-analyses is necessary to estimate the effects of methodological characteristics, since individual meta-analyses may inaccurately estimate these effects.[12]

Some meta-epidemiological studies have been previously published. These studies evaluated the influence of methodological characteristics, such as allocation concealment and intention-to-treat (ITT) analysis on the treatment effects of clinical interventions in different healthcare areas.[6,12-14] Results from these studies demonstrated that trials with inadequate allocation concealment overestimated the treatment effects up to 18%.[6,12] Most of the meta-analyses conclusions are likely to change if only trials with adequate allocation concealment were included. It has been reported that 69% of meta-analysis were no longer statistically significant when trials with unclear or inadequate

allocation concealment were excluded.[15] In contrast, the influence of performing ITT analysis (or attrition bias) on the effect estimates of RCTs is still unclear.[12,14,16]

Most meta-epidemiological studies derived from reports of RCTs are from the field of medicine. These studies are likely to be different from physical therapy trials, especially regarding the type of intervention and outcomes assessed.[17] To date, there is only one meta-epidemiological study published that evaluated the relationship between methodological characteristics and the treatment effects of physical therapy interventions.[17] This study included different areas of physical therapy and therefore, selecting a wide range of different clinical conditions, leading to a large level of heterogeneity that may hamper the association between the characteristics assessed and treatment effects. Thus, we choose to focus on low back pain trials. Besides being the most prevalent, costly and disabling musculoskeletal condition, low back pain is the musculoskeletal condition with largest number of clinical trials in the literature.[18-20]

The lack of meta-epidemiological studies in the literature that have evaluated the association between methodological characteristics and the treatment effects of interventions in low back pain trials motivated us to conduct this study.

OBJECTIVES

The objectives of this study are: (1) to establish if adequate allocation concealment and the use of intention to treat analysis influence the effect size of physical therapy interventions in meta-analyses of low back pain RCTs when compared with meta-analyses of trials without these characteristics; (2) to evaluate if allocation concealment process and intention to treat analyses are evaluated and reported adequately in clinical trials.

METHODS

Study design

Protocol of a meta-epidemiological study

Protocol and registration

The protocol was prospectively registered at the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42016052347. We followed the Preferred Reporting Items for Systematic review and Meta-Analyses Protocols (PRISMA - P)[21] guidelines and the checklist is available (see appendix 1).

Identification and selection of studies

All meta-analyses of randomized controlled trials evaluating treatment of non-specific low back pain will be included in this study. Non-specific low back pain is defined as low back pain not attributed to a specific pathology, such as nerve root compromise or serious spinal pathology.[22] We will include meta-analyses composed of RCTs comparing physical therapy interventions in adult patients with non-specific low back pain with placebo or no intervention, and have pain intensity measured by continuous measures (such as the 11-point numerical rating scale) or disability (such as the Rolland-Morris Disability Questionnaire or Oswestry Disability Index) as the main outcomes. Any meta-analysis with mixed populations will be excluded. Overview of reviews will also not be included in our study. In the case of Cochrane reviews, if there are multiple versions of the same review (i.e., updates), we will include only the most recent one.

Identification of studies to be included will be done through an electronic search without language restriction and publication date in the following databases: PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Embase via OvidSP, Cochrane Database of Systematic Reviews (http://www.cochranelibrary.com/) and PEDro

(http://pedro.org.au/). The search strategy will combine validated filters related to meta-analyses and systematic reviews with physical therapy interventions on low back pain (See appendix 2 for more details). Two review authors will independently assess and select potential studies to be included based on titles and abstracts. Any discordance will be solved by consensus, and if necessary, a third evaluator will arbitrate the final decision. Full-texts of selected articles will be collected and evaluated in the same manner.

Risk of bias assessment (selection and attrition bias)

We will extract the information about selection (allocation concealment) and attrition bias (use of intention to treat analysis) from the Physiotherapy Evidence Database (PEDro) for each RCT.[23] The definitions used by the PEDro database about these domains are: *allocation concealment process is considered adequate, if the responsible for assignment has no information about participants included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the participant (such as, use of sequentially sealed opaque envelops or "off-site" allocation)*; *ITT analysis means that all participants were analyzed in the groups to which they were originally allocated.*[23] When the score of domain bias from an included article is not available at PEDro database, two review authors will independently assess it, following the same recommendations stated above. Any disagreements will be resolved by discussion or arbitration by a third reviewer when consensus cannot be reached.

Data extraction and synthesis

Two review authors will independently extract data from selected systematic reviews using a standardized extraction form. Any discordance will also be resolved by discussion or arbitration by a third reviewer when consensus cannot be reached.

We will extract bibliographic data (authors, title and year of publication), study characteristics (design, sample size and intervention used), characteristics of the participants (gender, age, duration and severity of the condition), results of studies included in the meta-analysis (mean and standard deviation). We will only extract outcomes from the short-term follow-up (closest to 4 weeks). E-mail requests will be sent to trial authors for additional information data, when necessary.

Data analysis and synthesis

In order to determine whether allocation concealment and ITT analysis affect treatment effect of interventions, a two-level analysis will be conducted. Initially, the effect size of each study will be calculated by dividing the mean difference between groups by the standard deviation values.[24] A negative effect size indicates a beneficial effect of the experimental intervention. Individual study data will be retrieved from the meta-analyses included in our study.

After that, we will calculate two pooled effect size for each meta-analysis by using a random effect model: one corresponding to the pooled effect size from studies with the characteristics of interest (allocation concealment and ITT analysis) and the other for studies without these characteristics. A negative difference in effect size indicates a beneficial effect of studies without the characteristics of interest for the experimental group. We will assess between-trial heterogeneity using I-squared test (I^2). This test demonstrates whether the percentage of total variation across studies is explained by heterogeneity rather than chance. An I^2 higher than 75% will be considered as 'high heterogeneity', an I^2 of 50% to 75% will be considered as 'moderate heterogeneity', and an I^2 lower than 25% will be considered as 'low heterogeneity'.[25] Review Manager (RevMan) version 5 software will be used for all meta-analyses and heterogeneity assessment.

The second-level analysis will be a meta-regression to evaluate the association between characteristics of included studies and effect size. The dependent variable will the effect size (mean between-group difference) for the main outcomes (pain or disability), while the independent variables will the methodological characteristics of interest (allocation concealment and ITT analysis). Additionally, we will use three independent covariates in meta-regression analysis: sample size, sequence generation and heterogeneity. The sample size will be classified as 'small' (< 100 patients randomized per arm) or 'high' (≥ 100 patients randomized per arm).[26] Sequence generation is considered adequate when subjects were randomly allocated to groups (e.g., computer-generated random numbers; coin-tossing and dice-rolling).[23] For the heterogeneity assessment, we will adopt the classification described above. The covariates will be used according to the number of studies included. For each 10 trials, one covariate will be incorporated to the analysis. Random-effects meta-regression will be conducted using the 'metareg' command in STATA 10 and weighted using effect size standard errors.

DISCUSSION

To our knowledge, this is the first study aimed to investigate if meta-analyses' findings and the magnitude of the effect sizes of physical therapy intervention in low back pain RCTs could be influenced by methodological features (i.e., allocation concealment and ITT analysis). Meta-analyses from RCTs are responsible for the most reliable evidence on the treatment of patients with low-back pain, and its results are of interest to a range of stakeholders. However, biased results from RCTs can lead to inadequate clinical decision making and consequently affect patient outcomes.

Therefore, we believe that the findings of this meta-epidemiological study will provide important contributions to clinicians, researchers, and policy-makers in the low-back pain field. This study will improve the available evidence for physical therapists, through the disclosure of reliable and unbiased results on clinical decision-making. It will also help promoting better politics of evidence-based in this area by detecting possible issues while interpreting trials of physical therapy interventions for patients with back pain.

The present meta-epidemiological study has some strength points. Since this approach is such similar to a systematic review, we will approach strictly methods to identify and select studies to be included through defined inclusion criteria and sensitive search strategy. Data extraction and analysis will be also performed by rigorous methods to avoid potential bias in this study.

The limitation of the present study is the fact that it is restricted to meta-analyses of physical therapy interventions in non-specific low back pain. Thus, our results may have limited generalizability to other interventions as well as other clinical conditions.

Dissemination

We intend to disseminate our results through presentations at national and international conferences (e.g., World Confederation for Physical Therapy and International Back and Neck Pain Forum) as well as publishing our study in a high-impact international scientific journal.

COMPETING INTEREST

None

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APPENDIX 2 – Search strategy for each database

Pubmed

1 dorsalgia.ti,ab,kw.

2 exp Back Pain/

3 "backache" ti,ab

4 (lumbar adj pain) ti,ab

5 coccyx.ti,ab

6 coccydynia.ti,ab

7 sciatica.ti,ab

8 exp sciatic neuropathy/

9 "spondylosis" ti,ab

10 "lumbago" ti,ab

11 lumbago.ti,ab,kw.

12 (disc adj degeneration) ti,ab

13 (disc adj prolapse) ti,ab

14 (disc adj herniation) ti,ab

15 OR / #1-14

16 systematic review /

17 meta-analysis /

18 (#16 OR #17)

19 (#15 AND #19)

Embase

1 dorsalgia.ti,ab,kw.

2 (back pain or backache or back ache).ti,ab,kw.

3 exp LOW BACK PAIN/

4 exp BACKACHE/

5 (lumb$ adj3 pain).ti,ab,kw.

6 coccyx.ti,ab,kw.

7 coccydynia.ti,ab,kw.

8 sciatica.ti,ab,kw.

9 sciatica/

10 exp ISCHIALGIA/

11 spondylosis.mp.

12 lumbago.ti,ab,kw.

13 back disorder$.ti,ab,kw.

14 or/1-13

15 systematic review /

16 meta-analysis /

17 (#15 OR #16)

18 (#14 AND #17)

Cochrane Database of Systematic Reviews

#1 MeSH descriptor: [Back Pain] explode all trees

#2 dorsalgia

#3 backache or back ache

#4 MeSH descriptor: [Back Pain] explode all trees

#5 lumb* near pain or coccyx or coccydynia or sciatica or spondylosis

#6 MeSH descriptor: [Spine] explode all trees

#7 MeSH descriptor: [Spinal Diseases] explode all trees

#8 lumbago or discitis or disc near herniat*

#9 spinal fusion

#10 facet near joint*

#11 MeSH descriptor: [Intervertebral Disk] explode all trees

#12 postlaminectomy

#13 arachnoiditis

#14 failed near back

#15 MeSH descriptor: [Cauda Equina] explode all trees

#16 lumb* near vertebra*

#17 spinal near stenosis

#18 slipped near (disc* or disk*)

#19 degenerat* near (disc* or disk*)

#20 stenosis near (spine or root or spinal)

#21 displace* near (disc* or disk*)

#22 prolap* near (disc* or disk*)

#23 MeSH descriptor: [Sciatic Neuropathy] explode all trees

#24 sciatic*

#25 back disorder*

#26 back near pain

#27 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26)

#28 systematic review

#29 meta-analysis

#30 (#28 or #29)

#31 (#27 AND #30)

PEDro

Problem: Pain

AND

Body Part: lumbar spine, sacro-iliac joint or pelvis

AND

Method: systematic review

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X	☐	1-4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	X	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X	☐	53
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	☐	6-14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	☐	20-22
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	☐	X	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐	X	n/a
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	X	n/a
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X	☐	16-18
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X	☐	76-115
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to	X	☐	117-123

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		participants, interventions, comparators, and outcomes (PICO)			
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X	☐	134-145
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X	☐	146-150
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	X	☐	Appendix 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	☐	198-199 / 212-214
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X	☐	152-156
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X	☐	172-174
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X	☐	175-179
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X	☐	140-142
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	X	☐	157-170
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	☐	182-185
	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 (e.g., I^2, Kendall's tau)	X	☐	188-199

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X	☐	210-214
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	X	n/a
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	X	n/a
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	X	n/a

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AUTHORS' CONTRIBUTIONS

MOA, BTS, CM and LOPC conceived and designed the study. All of the authors assisted in the final protocol and agreed to its final approval before submission.

COMPETING INTEREST

None

ABSTRACT

Introduction: Meta-epidemiological studies examining the influence of methodological such as inadequate allocation concealment and lack of intention-to-treat analysis features have been performed in a large number of health-care areas. However, there are no studies investigating these biases in physical therapy interventions for patients with low back pain. The aim of this study is to investigate the influence of allocation concealment and the use of intention-to-treat analysis on estimates of the treatment effects of physical therapy interventions in low back pain clinical trials.

Methods and analysis: Searches on PubMed, Embase, Cochrane Database of Systematic Reviews, PEDro and CINAHL databases will be performed. We will search for systematic reviews that include a meta-analysis of randomised controlled trials that compared physical therapy interventions in patients with low back pain compared with placebo or no intervention, and have pain intensity or disability as the primary outcomes. Information about selection (allocation concealment) and attrition bias (intention-to-treat analysis) will be extracted from the PEDro Database for each included trial. Information about bibliographic data, study characteristics, participants' characteristics and study results will be extracted. A random effects model of meta-analyses will be used to pool the treatment effects comparing trials with allocation concealment and intention-to-treat analysis with those that did not include these features. A meta-regression will be performed to measure the association between methodological features and treatment effects considering each trial. The dependent variable will be the treatment effects (the mean between-group differences) for the primary outcomes (pain or disability), while the independent variables will be the methodological features of interest (allocation concealment and intention-to-treat analysis). Other covariates will include sample size and sequence generation.

Ethics and dissemination: No ethical approval will be required for this study. The study findings will be published in a peer-reviewed journal and presented at international conferences.

Registration number: PROSPERO (CRD42016052347).

Keywords: Epidemiologic Research Design; Low Back Pain; Physical Therapy Modalities

Strengths and limitations of this study

- This protocol was specified following the Preferred Reporting Items for Systematic review and Meta-Analyses Protocols (PRISMA - P) guidelines.
- This study will be the first one to evaluate the association between methodological characteristics and the treatment effects of physical therapy interventions in low back pain trials.
- The results from this meta-epidemiological study are likely to bring new insights to the physical therapy scientific community by informing issues that need to be considered in randomised trials.
- The findings from this meta-epidemiological study may have limited generalisability to other clinical conditions, since it is restricted to physical therapy treatment of low back pain.

INTRODUCTION

Systematic reviews and meta-analyses of randomised controlled trials are considered the 'gold standard' to evaluate the efficacy and effectiveness of healthcare interventions.[1,2] While systematic reviews and meta-analyses provide the best available evidence to support clinical decision-making and to promote changes in health policies, they are not free of bias.[3,4] The presence of potential biases in clinical trials, due to inadequate allocation concealment (selection bias) or lack of intention-to-treat analysis (attrition bias) may overestimate the effect size of the interventions.[5-8] These types of bias can directly influence the results from meta-analyses, leading to inaccurate conclusions, misleading clinicians and researchers.[9]

Meta-epidemiological studies are designed to understand the impact of study level characteristics (i.e., methodological quality, study design) in randomised clinical trials (RCTs), investigating the association between these specific study characteristics and the intervention effect estimates from collections of meta-analyses.[10,11] A collection of meta-analyses is necessary, since individual meta-analyses may inaccurately estimate these effects.[12]

Some meta-epidemiological studies have been previously published. These studies evaluated the influence of methodological characteristics, such as allocation concealment and intention-to-treat (ITT) analysis on the treatment effects of clinical interventions in different healthcare areas.[6,12-14] Results from these studies demonstrated that trials with inadequate allocation concealment overestimated the treatment effects up to 18%.[6,12] Most of the meta-analyses conclusions are likely to change if only trials with adequate allocation concealment were included. It has been reported that 69% of meta-analyses were no longer statistically significant when trials with unclear or inadequate

allocation concealment were excluded.[15] In contrast, the influence of performing ITT analysis (or attrition bias) on the effect estimates of RCTs is still unclear.[12,14,16]

Most meta-epidemiological studies derived from reports of RCTs are from the field of medicine. These studies are likely to be different from physical therapy trials, especially regarding the type of intervention and outcomes assessed.[17] To date, there is only one meta-epidemiological study published that evaluated the relationship between methodological characteristics and the treatment effects of physical therapy interventions.[17] This study included different areas of physical therapy and therefore, selecting a wide range of different clinical conditions, leading to a large level of heterogeneity that may hamper the association between the characteristics assessed and treatment effects. Therefore, we chose to focus on low back pain trials. Besides being the most prevalent, costly and disabling musculoskeletal condition, low back pain is the musculoskeletal condition with largest number of clinical trials in the physiotherapy literature.[18-21]

The lack of meta-epidemiological studies that have evaluated the association between methodological characteristics and the treatment effects of interventions in low back pain trials motivated us to conduct this study.

OBJECTIVES

The objectives of this study are: (1) to establish if adequate allocation concealment and the use of intention to treat analysis influence the treatment effects of physical therapy interventions in systematic reviews with meta-analysis of low back pain RCTs when compared with systematic reviews with meta-analysis of trials without these characteristics; (2) to evaluate if allocation concealment and intention to treat analyses are evaluated and reported adequately in clinical trials.

METHODS

Study design

This is a protocol of a meta-epidemiological study.

Protocol and registration

The protocol was prospectively registered at the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42016052347. We followed the Preferred Reporting Items for Systematic review and Meta-Analyses Protocols (PRISMA - P)[22] guidelines and the checklist is available (see appendix 1).

Identification and selection of studies

All RCTs included in systematic reviews with meta-analysis evaluating physical therapy treatment in adults with non-specific low back pain that included pain or disability (as continuous variables) as the main outcomes will be included in this study. Non-specific low back pain is defined as low back pain not attributed to a specific pathology, such as nerve root compromise or serious spinal pathology.[23] The physical therapy intervention will be compared with placebo or no intervention. We will consider all possible meta-analyses from the same systematic review, since a systematic review may contain more than one meta-analysis (e.g different outcomes). Any systematic reviews with meta-analysis with mixed populations will not be considered. Overview of reviews will also not be considered in our study. In the case of Cochrane reviews, if there are multiple versions of the same review (i.e., updates), we will consider only the most recent one.

Potentially eligible studies to be included will be retrieved through an electronic search in the following databases from their inception up to February 2017: PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Embase via OvidSP, Cochrane Database of

Systematic Reviews (http://www.cochranelibrary.com/), PEDro (http://pedro.org.au/) and CINAHL (https://health.ebsco.com/products/the-cinahl-database). There will be no restriction to language of studies. The search strategy will combine validated filters related to systematic reviews and meta-analyses with physical therapy interventions on low back pain (See appendix 2 for more details). Two review authors will independently assess and select potential studies to be included based on titles and abstracts. Any discordance will be solved by consensus, and if necessary, a third evaluator will arbitrate the final decision. Full-texts of selected articles will be collected and evaluated in the same manner. After the process of identification and selection, we will retrieve the full-texts to extract the data. Two authors from our study are raters of the PEDro database, so it will be possible to obtain the full texts that are indexed on this database. It is important to state that about 92% of physical therapy RCTs are indexed on the PEDro database. [24] For those RCTs not indexed on PEDro, we will make all efforts to get these full texts (searching other databases, contact authors).

Risk of bias assessment (selection and attrition bias)

We will extract the information about selection (allocation concealment) and attrition bias (intention to treat analysis) from the Physiotherapy Evidence Database (PEDro) for all trials included in the systematic reviews.[25] We decided to use the PEDro scale due to the following reasons: 1) the PEDro scale has high reliability for individual ratings and consensus ratings and can be used as a continuous scale for measuring the methodological quality of trials;[25,26] 2) the PEDro scale is strongly correlated (r=0.83; 95% CI 0.76 to 0.88) with the Cochrane Risk of Bias tool;[27] and 3) Feasibility: as two authors from this study are raters from the PEDro database, we can easily download the PEDro scores for the included RCTs in our study. The definitions used by the PEDro

database about these domains are: *allocation concealment process is considered adequate, if the responsible for assignment has no information about participants included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the participant (such as, use of sequentially sealed opaque envelops or "off-site" allocation)*; *ITT analysis means that all participants were analyzed in the groups to which they were originally allocated.*[25] Each domain will be rated as 'yes', when the criterion is clearly satisfied, or 'no' when the criterion is not satisfied or the information is unclear in the text. When the score of domain bias from an included article is not available at the PEDro database (the article may not be indexed in PEDro database; or the article may be in process to be rated), two assessors, not involved in the study, will independently assess it, following the same recommendations stated above. Any disagreements will be resolved by discussion or arbitration by a third assessor when consensus cannot be reached. The assessors are trained raters of the PEDro scale that work in our department and will be blinded to the scope of the manuscript.

Data extraction and synthesis

Two review authors will independently extract data from all trials included in the selected systematic reviews using a standardized extraction form. Any discordance will also be resolved by discussion or arbitration by a third reviewer when consensus cannot be reached.

We will extract bibliographic data (authors, title and year of publication), study characteristics (design, sample size and intervention used), characteristics of the participants (gender, age, duration and severity of the condition), outcomes results (mean and standard deviation). We will only extract outcomes results from the short-term follow-up (closest to 4 weeks). E-mail requests will be sent to trial authors for additional information data, when necessary.

Data analysis and synthesis

In order to determine whether allocation concealment and ITT analysis affect estimates of treatment effect, a two-level analysis will be conducted. Individual trial data will be retrieved from the meta-analyses included in our study. Initially, the treatment effects of each trial will be calculated using mean differences (MD) with 95% confidence intervals for between-group differences at short-term follow-up, or for between-group differences in change scores.[28,29] Data will be converted to a common 0 to 100-point scale if trials had evaluated the same outcome on different scales. Data will be presented separately for each outcome of interest (pain and disability).

After establishing the treatment effects for the trials included, we will calculate a pooled treatment effect estimate for each meta-analysis by using a random effects model: one corresponding to the pooled effect size from trials with the characteristics of interest (allocation concealment and ITT analysis) and the other for studies without these characteristics for each outcome. Data will be presented separately for each characteristic of interest. After calculating meta-analyses with individual trial data, we will calculate the difference in treatment effects between trials with the characteristics of interest (allocation concealment and ITT analysis) and those without these characteristics.

We will assess between-trial heterogeneity using I-squared test (I^2). This test demonstrates whether the percentage of total variation across studies is explained by heterogeneity rather than chance. An I^2 higher than 75% will be considered as 'high heterogeneity', an I^2 of 50% to 75% will be considered as 'moderate heterogeneity', and an I^2 lower than 25% will be considered as 'low heterogeneity'.[30] Review Manager (RevMan) version 5 software will be used for all meta-analyses and heterogeneity assessment.

The second stage of the analysis will be a meta-regression to evaluate the association between methodological characteristics of included trials and the treatment effects.[11] The dependent variable will be the treatment effects (mean between-group difference) for the main outcomes (pain or disability), while the independent variables will the methodological characteristics of interest (allocation concealment and ITT analysis). Additionally, we will use two independent covariates in meta-regression analysis: sample size and sequence generation. We decided to investigate the effect of sequence generation and sample size since these variables have been associated with treatment effect estimates.[31] Sequence generation assessment is considered adequate when subjects were randomly allocated to groups (e.g., computer-generated random numbers; coin-tossing and dice-rolling).[25] The sample size will be considered as a continuous quantitative variable in the meta-regression model. The covariates will be used according to the number of studies included. For each 10 trials, one covariate will be incorporated to the analysis. Random-effects meta-regression will be conducted using the 'metareg' command in STATA 10 and weighted using effect size standard errors.[11]

DISCUSSION

To our knowledge, this is the first study aimed to investigate if meta-analyses' findings and the magnitude of the treatment effects of physical therapy interventions in low back pain RCTs could be influenced by methodological features (i.e., allocation concealment and ITT analysis). Meta-analyses from RCTs are responsible for the most reliable evidence on the treatment of patients with low-back pain, and its results are of interest to a range of stakeholders.

However, biased results from RCTs can lead to inadequate clinical decision-making and consequently affect patient outcomes. Clinicians may select interventions for their patients based on trials results that are inflated, and so these are not a very reliable guide to treatment selection. For example, a systematic review about the effectiveness of low level laser therapy for chronic LBP found a significantly greater reduction in pain in response to laser therapy compared to placebo.[32] However, this finding was based on a meta-analysis with three clinical trials that did not conceal allocation or use an ITT analysis, so this result could be an overestimate of the true effect of laser. If this premise of overestimated effect is true, clinicians might in good faith select interventions that might not help their patients.

Therefore, we believe that the findings of this meta-epidemiological study will provide important contributions to clinicians, researchers, and policy-makers in the low-back pain field. This study will improve the available evidence for physical therapists, through the disclosure of reliable and unbiased results on clinical decision-making. It will also help promoting better politics of evidence-based in this area by detecting possible issues while interpreting trials of physical therapy interventions for patients with back pain.

The present meta-epidemiological study has a number of strengths. Since this approach is similar to a systematic review, we will pre-specify methods to identify and select studies to be included through pre-defined inclusion criteria and sensitive search strategy. Data extraction and analysis will be also performed by rigorous methods to avoid potential bias in this study.

The limitation of the present study is the fact that it is restricted to meta-analyses of physical therapy interventions in non-specific low back pain. Thus, our results may

have limited generalizability to other interventions as well as to other clinical conditions.

Dissemination

We intend to disseminate our results through presentations at national and international conferences (e.g., World Confederation for Physical Therapy and International Back and Neck Pain Forum) as well as publishing our study in a high-impact international scientific journal.

COMPETING INTEREST

None

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APPENDIX 2 – PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X	☐	1-5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	X	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X	☐	57
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	☐	6-14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	☐	20-22
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	☐	X	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	X	☐	16-19
Sponsor	5b	Provide name for the review funder and/or sponsor	X	☐	16-19
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X	☐	16-19
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X	☐	79-119
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X	☐	121-127

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X	☐	137-149
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X	☐	150-157
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	X	☐	Appendix 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	☐	193-194
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X	☐	157-161
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X	☐	192-196
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X	☐	197-200
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X	☐	139-140
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	X	☐	168-191
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	☐	203-211
	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 (e.g., I^2, Kendall's tau)	X	☐	212-227
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X	☐	228-243
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	X	n/a
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective	☐	X	n/a

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		reporting within studies)			
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	**X**	n/a

APPENDIX 2 – Search strategy for each database

Pubmed

1 dorsalgia.ti,ab,kw.

2 exp Back Pain/

3 “backache” ti,ab

4 (lumbar adj pain) ti,ab

5 coccyx.ti,ab

6 coccydynia.ti,ab

7 sciatica.ti,ab

8 exp sciatic neuropathy/

9 “spondylosis” ti,ab

10 “lumbago” ti,ab

11 lumbago.ti,ab,kw.

12 (disc adj degeneration) ti,ab

13 (disc adj prolapse) ti,ab

14 (disc adj herniation) ti,ab

15 OR / #1-14

16 systematic review /

17 meta-analysis /

18 (#16 OR #17)

19 (#15 AND #19)

Embase

1 dorsalgia.ti,ab,kw.

2 (back pain or backache or back ache).ti,ab,kw.

3 exp LOW BACK PAIN/

4 exp BACKACHE/

5 (lumb$ adj3 pain).ti,ab,kw.

6 coccyx.ti,ab,kw.

7 coccydynia.ti,ab,kw.

8 sciatica.ti,ab,kw.

9 sciatica/

10 exp ISCHIALGIA/

11 spondylosis.mp.

12 lumbago.ti,ab,kw.

13 back disorder$.ti,ab,kw.

14 or/1-13

15 systematic review /

16 meta-analysis /

17 (#15 OR #16)

18 (#14 AND #17)

Cochrane Database of Systematic Reviews

#1 MeSH descriptor: [Back Pain] explode all trees

#2 dorsalgia

#3 backache or back ache

#4 MeSH descriptor: [Back Pain] explode all trees

#5 lumb* near pain or coccyx or coccydynia or sciatica or spondylosis

#6 MeSH descriptor: [Spine] explode all trees

#7 MeSH descriptor: [Spinal Diseases] explode all trees

#8 lumbago or discitis or disc near herniat*

#9 spinal fusion

#10 facet near joint*

#11 MeSH descriptor: [Intervertebral Disk] explode all trees

#12 postlaminectomy

#13 arachnoiditis

#14 failed near back

#15 MeSH descriptor: [Cauda Equina] explode all trees

#16 lumb* near vertebra*

#17 spinal near stenosis

#18 slipped near (disc* or disk*)

#19 degenerat* near (disc* or disk*)

#20 stenosis near (spine or root or spinal)

#21 displace* near (disc* or disk*)

#22 prolap* near (disc* or disk*)

#23 MeSH descriptor: [Sciatic Neuropathy] explode all trees

#24 sciatic*

#25 back disorder*

#26 back near pain

#27 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26)

#28 systematic review

#29 meta-analysis

#30 (#28 or #29)

#31 (#27 AND #30)

PEDro

Problem: Pain

AND

Body Part: lumbar spine, sacro-iliac joint or pelvis

AND

Method: systematic review

CINAHL

S1 "lumbago"

S2 (MH "Spondylolisthesis") OR (MH "Spondylolysis")

S3 (MH "Thoracic Vertebrae")

S4 S1 or S2 or S3

S5 lumbar N2 vertebra

S6 (MH "Lumbar Vertebrae")

S7 "coccydynia"

S8 "coccyx"

S9 "sciatica"

S10 (MH "Sciatica")

S11 (MH "Coccyx")

S12 S5 or S6 or S7or S8 or S9 or S10 or S11

S13 backache or "back ache"

S14 lumb* W3 pain

S15 back pain

S16 (MH "Low Back Pain")

S17 (MH "Back Pain+")

S18 "dorsalgia"

S19 S13 S14 or S15 or S16 or S17 or S18 or S34

S20 S4 or S12 or S19

S21 systematic review

S22 meta-analysis

S23 S21 or S22

S24 S20 and S23

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X	☐	1-5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	X	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X	☐	57
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	☐	6-14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	☐	20-22
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	☐	X	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	X	☐	16-19
Sponsor	5b	Provide name for the review funder and/or sponsor	X	☐	16-19
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X	☐	16-19
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X	☐	79-119
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to	X	☐	121-127

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		participants, interventions, comparators, and outcomes (PICO)			
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X	☐	137-149
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X	☐	150-157
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	X	☐	Appendix 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	☐	193-194
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X	☐	157-161
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X	☐	192-196
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X	☐	197-200
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X	☐	139-140
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	X	☐	168-191
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	☐	203-211
	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 (e.g., I^2, Kendall's tau)	X	☐	212-227
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	X	☐	228-243

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		regression)			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	X	n/a
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	X	n/a
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	X	n/a

BMJ Open

THE INFLUENCE OF ALLOCATION CONCEALMENT AND INTENTION-TO-TREAT ANALYSIS ON TREATMENT EFFECTS OF PHYSICAL THERAPY INTERVENTIONS IN LOW BACK PAIN RANDOMIZED CONTROLLED TRIALS: A PROTOCOL OF A META-EPIDEMIOLOGICAL STUDY

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AUTHORS' CONTRIBUTIONS

MOA, BTS, CM and LOPC conceived and designed the study. All authors reviewed the final protocol and agreed to its final approval before submission.

COMPETING INTEREST

None

ABSTRACT

Introduction: Meta-epidemiological studies examining the influence of methodological characteristics, such as allocation concealment and intention-to-treat analysis have been performed in a large number of health-care areas. However, there are no studies investigating these characteristics in physical therapy interventions for patients with low back pain. The aim of this study is to investigate the influence of allocation concealment and the use of intention-to-treat analysis on estimates of treatment effects of physical therapy interventions in low back pain clinical trials.

Methods and analysis: Searches on PubMed, Embase, Cochrane Database of Systematic Reviews, PEDro and CINAHL databases will be performed. We will search for systematic reviews that include a meta-analysis of randomized controlled trials that compared physical therapy interventions in patients with low back pain with placebo or no intervention, and have pain intensity or disability as the primary outcomes. Information about selection (allocation concealment) and attrition bias (intention-to-treat analysis) will be extracted from the PEDro Database for each included trial. Information about bibliographic data, study characteristics, participants' characteristics and study results will be extracted. A random effects model will be used to provide separate estimates of treatment effects for trials with and without allocation concealment and with and without intention to treat analysis (e.g., four estimates). A meta-regression will be performed to measure the association between methodological features and treatment effects from each trial. The dependent variable will be the treatment effect (the mean between-group differences) for the primary outcomes (pain or disability), while the independent variables will be the methodological features of interest (allocation concealment and intention-to-treat analysis). Other covariates will include sample size and sequence generation.

Ethics and dissemination: No ethical approval will be required for this study. The study findings will be published in a peer-reviewed journal and presented at international conferences.

Registration number: PROSPERO (CRD42016052347).

Keywords: Epidemiologic Research Design; Low Back Pain; Physical Therapy Modalities

Strengths and limitations of this study

- This protocol was specified following the Preferred Reporting Items for Systematic review and Meta-Analyses Protocols (PRISMA - P) guidelines.
- This study will be the first to evaluate the association between methodological characteristics and estimates of the treatment effects of physical therapy interventions in low back pain trials.
- The results from this meta-epidemiological study are likely to bring new insights to the physical therapy scientific community by informing issues that need to be considered in randomized trials.
- The findings from this meta-epidemiological study may have limited generalizability to other clinical conditions, since it is restricted to physical therapy treatment of low back pain.

INTRODUCTION

Systematic reviews and meta-analyses of randomized controlled trials are considered the 'gold standard' to evaluate the efficacy and effectiveness of healthcare interventions.[1,2] While systematic reviews and meta-analyses provide the best available evidence to support clinical decision-making and to promote changes in health policies, they are not free of bias.[3,4] The presence of potential biases in clinical trials, due to inadequate allocation concealment (selection bias) or lack of intention-to-treat analysis (attrition bias) may lead to inflated estimates of treatment effect.[5-8] These types of bias can directly influence the results from meta-analyses, leading to inaccurate conclusions, misleading clinicians and researchers.[9]

Meta-epidemiological studies are designed to understand the impact of study level characteristics (e.g., methodological quality, study design) in randomized controlled trials (RCTs), investigating the association between these specific study characteristics and the intervention effect estimates from collections of meta-analyses.[10,11] Previous meta-epidemiological studies have evaluated the influence of methodological characteristics, such as allocation concealment and intention-to-treat (ITT) analysis on the treatment effects of clinical interventions in different healthcare areas.[6,12-14] The result of a combined analysis of meta-epidemiological studies demonstrated that trials with inadequate or unclear allocation concealment overestimated the treatment effects up to 7%.[15] This means that the conclusions of meta-analyses are likely to change if restricted to trials with adequate allocation concealment. It has been reported that 69% of meta-analyses were no longer statistically significant when trials with unclear or inadequate allocation concealment were excluded.[16]

Deviation from ITT analysis is common in systematic reviews and RCTs. A study of 222 systematic reviews reported that 36% included at least one trial that

deviated from ITT.[17] However, the influence of performing ITT analysis on the effect estimates of RCTs is still unclear.[13,14,18] The direction and magnitude of the influence of performing ITT analysis may vary between studies according to different methods and definitions used. For example, Dossing et al[19] classified trials as ITT analysis or 'modified ITT' analysis. They classified trials as using an ITT analysis if all randomized patients were included in analysis, including both patients with clinical outcome data and patients with imputed outcome data; and 'modified ITT' analysis if some individuals were excluded from the analyses despite the authors of the trial referring to it as being ITT. No significant difference in the treatment effect was found between trials that performed ITT analysis compared to 'modified ITT' analysis. In contrast, Abraha et al[20], using a different definition for deviation from ITT analysis without taking into account the occurrence of post-randomization exclusions, found that the treatment effect of trials that performed 'modified ITT' analysis was inflated by 17% compared to trials that performed ITT analysis.

Most meta-epidemiological studies derived from reports of RCTs are from the field of medicine. These studies are likely to be different from physical therapy trials, especially regarding the type of intervention and outcomes assessed.[21] To date, there is only one meta-epidemiological study published that evaluated the relationship between methodological characteristics and estimates of treatment effect of physical therapy interventions.[21] This study included different areas of physical therapy and therefore, selecting a wide range of different clinical conditions, leading to a large level of heterogeneity that may hamper the association between the characteristics assessed and treatment effects. Therefore, we chose to focus on low back pain trials. Besides being the most prevalent, costly and disabling musculoskeletal condition, low back pain is the

musculoskeletal condition with largest number of clinical trials in the physical therapy literature.[22-25]

The lack of meta-epidemiological studies that have evaluated the association between methodological characteristics and the treatment effects of interventions in low back pain trials motivated us to conduct this study.

OBJECTIVES

The objectives of this study are: (1) to establish if adequate allocation concealment and the use of ITT analysis influence the estimates of treatment effect of physical therapy interventions in low back pain RCTs and (2) to evaluate if allocation concealment and ITT analysis are evaluated and reported adequately in clinical trials.

METHODS

Study design

This is a protocol of a meta-epidemiological study.

Protocol and registration

The protocol was prospectively registered at the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42016052347. We followed the Preferred Reporting Items for Systematic review and Meta-Analyses Protocols (PRISMA - P)[26] guidelines and the checklist is available (see appendix 1).

Identification and selection of studies

All RCTs included in systematic reviews with meta-analysis evaluating physical therapy treatment in adults with non-specific low back pain that included pain or disability (as continuous variables) as the main outcomes will be included in this study. Non-specific low back pain is defined as low back pain not attributed to a specific

pathology, such as nerve root compromise or serious spinal pathology.[27] The physical therapy intervention will be compared with placebo or no intervention. We will consider all possible meta-analyses from the same systematic review, since a systematic review may contain more than one meta-analysis (e.g. different outcomes). Meta-analyses with only one trial will be excluded. Any systematic reviews with meta-analysis with mixed populations will not be considered. Overview of reviews will also not be considered in our study. In the case of Cochrane reviews, if there are multiple versions of the same review (e.g., updates), we will consider only the most recent one.

Potentially eligible systematic reviews to be included will be retrieved through an electronic search in the following databases from their inception up to February 2017: PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Embase via OvidSP, Cochrane Database of Systematic Reviews (http://www.cochranelibrary.com/), PEDro (http://pedro.org.au/) and CINAHL (https://health.ebsco.com/products/the-cinahl-database). There will be no restriction to language of studies. The search strategy will combine validated filters related to 'systematic reviews and meta-analyses', 'physical therapy interventions' and 'low back pain' (See appendix 2 for more details). Two review authors will independently assess and select potential studies to be included based on titles and abstracts. Any discordance will be resolved by consensus, and if necessary, a third assessor will arbitrate the final decision. Full-texts of selected systematic reviews will be collected and evaluated in the same manner. After the process of identification and selection, we will screen the systematic reviews for meta-analyses that fulfill our inclusion criteria. Once we have selected the systematic reviews with the meta-analyses to be included in our study, we will look for the full texts of the RCTs included on these meta-analyses in order to extract their original data. Two authors from our study are trained raters of the PEDro database, so it will be possible to

obtain the full texts that are indexed on this database. It is important to state that about 92% of physical therapy RCTs are indexed on the PEDro database.[28] For those RCTs not indexed on PEDro, we will make all efforts to get these full texts (searching other databases, contact authors).

Risk of bias assessment (selection and attrition bias)

We will extract the information about selection (allocation concealment) and attrition bias (ITT analysis) from the Physiotherapy Evidence Database (PEDro) for all trials included in the systematic reviews.[29] We decided to use the PEDro scale due to the following reasons: 1) the PEDro scale has high reliability for individual ratings and consensus ratings and can be used as a continuous scale for measuring the methodological quality of trials;[29,30] 2) the PEDro scale is strongly correlated (r=0.83; 95% CI 0.76 to 0.88) with the Cochrane Risk of Bias tool;[31] and 3) feasibility: as two authors from this study are raters from the PEDro database, we can easily download the PEDro scores for the included RCTs in our study.

The definitions used by the PEDro database for these domains are: "*Concealed allocation means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was off-site"*; *"An intention to treat analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that*

all subjects received treatment or control conditions as allocated".[29] Each domain will be rated as 'yes', when the criterion is clearly satisfied, or 'no' when the criterion is not satisfied or the information is unclear in the text. For ITT classification, trials will be rated as 'yes' for ITT analysis, if they use the term 'intention to treat', and it is clear that all subjects received treatment or control conditions as allocated, or that subjects were analyzed according to their initial group allocation. When there are post-randomization exclusions, a trial will be rated as 'no' if the exclusion is on the basis of not receiving allocated treatment. There are some trials that exclude patients after randomization if authors subsequentially realize that the participant was not eligible for the trial.[32,33] In this specific case, the trials will be rated as 'yes'. Trials will be rated as 'no', if authors did not mention any intention to treat approach or reported the use of a modified intention to treat approach. However, if it is clear that there were no post-randomization exclusions and all subjects were analyzed according to their initial group allocation, it will be rated as 'yes'.

When PEDro score is not available at the PEDro database (the article may not be indexed in PEDro database; or the article may be in process to be rated), two assessors, not involved in the study, will independently assess it, using the PEDro rating protocol. Any disagreements will be resolved by discussion or arbitration by a third assessor when consensus cannot be reached. The assessors will be trained raters of the PEDro scale that work in our department and will be blinded to the scope of the manuscript.

Data extraction and synthesis

Two review authors will independently extract data from all trials included in the selected systematic reviews using a standardized extraction form. Any disagreements will also be resolved by discussion or arbitration by a third reviewer when consensus cannot be reached.

We will extract bibliographic data (authors, title and year of publication), study characteristics (sample size and interventions used), characteristics of the participants (gender, age, duration and severity of the condition), outcomes results (mean and standard deviation). We will only extract outcomes results for the short-term follow-up (closest to 4 weeks). E-mail requests will be sent to trial authors for additional information data, when necessary.

Data analysis and synthesis

In order to determine whether allocation concealment and ITT analysis affect estimates of treatment effect, a two-level analysis will be conducted. Individual trial data will be retrieved from the meta-analyses included in our study. Initially, the treatment effects of each trial will be calculated using mean differences (MD) with 95% confidence intervals for between-group differences at short-term follow-up, or for between-group differences in change scores.[34,35] Data will be converted to a common 0 to 100-point scale if trials had evaluated the same outcome on different scales. Data will be presented separately for each outcome of interest (pain and disability).

After establishing the treatment effects for the trials included, we will calculate four pooled treatment effect estimates using a random effects model: (i) trials with allocation concealment, (ii) trials without allocation concealment, (iii) trials with ITT analysis and (iv) trials without ITT analysis. This will be done separately for pain and disability outcomes (e.g., a total of eight estimates).

We will assess between-trial heterogeneity using I-squared test (I^2). This test demonstrates whether the percentage of total variation across studies is explained by heterogeneity rather than chance. An I^2 higher than 75% will be considered as 'high heterogeneity', an I^2 of 50% to 75% will be considered as 'moderate heterogeneity', and an I^2 lower than 25% will be considered as 'low heterogeneity'.[36] Review Manager

(RevMan) version 5 software will be used for all meta-analyses and heterogeneity assessment.

The second stage of the analysis will be a meta-regression to evaluate the association between methodological characteristics of included trials and the estimates of treatment effect.[11] The dependent variable will be the treatment effects (mean between-group difference) for the main outcomes (pain or disability), while the independent variables will be the methodological characteristics of interest (allocation concealment and ITT analysis). Additionally, we will add two independent covariates in meta-regression analysis: sample size and sequence generation. We decided to investigate the effect of sequence generation and sample size since these variables have been associated with treatment effect estimates.[37] We will extract the information about sequence generation from the PEDro database and is defined as adequate if "subjects were randomly allocated to groups" (e.g., computer-generated random numbers; coin-tossing and dice-rolling).[29] It will be rated as 'yes', when the criterion is clearly satisfied, or 'no' when the criterion is not satisfied or the information is unclear in the text. The sample size will be considered as a continuous quantitative variable in the meta-regression model. The covariates will be used according to the number of studies included (e.g. one covariate for every ten trials). Random-effects meta-regression will be conducted using the 'metareg' command in STATA 10 and weighted using effect size standard errors.[11]

DISCUSSION

To our knowledge, this will be the first study aimed to investigate if the magnitude of the treatment effects of physical therapy interventions in low back pain RCTs is influenced by methodological characteristics (e.g., allocation concealment and

ITT analysis). Meta-analyses from RCTs are responsible for the most reliable evidence on the treatment of patients with low-back pain, and their results are of interest to a range of stakeholders.

However, biased results from RCTs can lead to inadequate clinical decision-making and consequently affect patient outcomes. Clinicians may select interventions for their patients based on trials results that are inflated, and so these are not a very reliable guide to treatment selection. For example, a systematic review about the effectiveness of low level laser therapy for chronic LBP found a significantly greater reduction in pain in response to laser therapy compared to placebo.[38] However, this finding was based on a meta-analysis with three clinical trials that did not conceal allocation or use an ITT analysis, so this result could be an overestimate of the true effect of laser. If this premise of overestimated effect is true, clinicians might in good faith select interventions that are unlikely to help their patients.

Therefore, we believe that the findings of this meta-epidemiological study will provide important contributions to clinicians, researchers, and policy-makers in the low-back pain field. This study will improve the available evidence for physical therapists, through the disclosure of reliable and unbiased results on clinical decision-making.

The present meta-epidemiological study has several strengths. Since this approach is similar to a systematic review, we will pre-specify methods to identify and select studies to be included through pre-defined inclusion criteria and sensitive search strategy. Data extraction and analysis will be also performed by rigorous methods to avoid potential bias in this study.

The limitation of the present study is that it is restricted to meta-analyses of physical therapy interventions in non-specific low back pain. Thus, our results may

have limited generalizability to other interventions as well as to other clinical conditions.

Dissemination

We intend to disseminate our results through presentations at national and international conferences (e.g., World Confederation for Physical Therapy and International Back and Neck Pain Forum) as well as publishing our study in a high-impact international scientific journal.

COMPETING INTEREST

None

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APPENDIX 1 – PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X	☐	1-5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	X	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X	☐	54
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	☐	6-14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	☐	20-22
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	☐	X	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	X	☐	16-19
Sponsor	5b	Provide name for the review funder and/or sponsor	X	☐	16-19
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X	☐	16-19
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X	☐	79-131
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X	☐	133-137

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X	☐	147-159
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X	☐	160-167
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	X	☐	Appendix 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	☐	171-174
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X	☐	167-171
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X	☐	223-226
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X	☐	227-232
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X	☐	149-150
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	X	☐	181-221
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	☐	234-246
	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 (e.g., I^2, Kendall's tau)	X	☐	247-251
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X	☐	254-271
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	X	n/a
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective	☐	X	n/a

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		reporting within studies)			
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	**X**	n/a

APPENDIX 2 – Search strategy for each database

Pubmed

1 dorsalgia.ti,ab,kw.

2 exp Back Pain/

3 “backache” ti,ab

4 (lumbar adj pain) ti,ab

5 coccyx.ti,ab

6 coccydynia.ti,ab

7 sciatica.ti,ab

8 exp sciatic neuropathy/

9 “spondylosis” ti,ab

10 “lumbago” ti,ab

11 lumbago.ti,ab,kw.

12 (disc adj degeneration) ti,ab

13 (disc adj prolapse) ti,ab

14 (disc adj herniation) ti,ab

15 OR / #1-14

16 systematic review /

17 meta-analysis /

18 (#16 OR #17)

19 (#15 AND #19)

Embase

1 dorsalgia.ti,ab,kw.

2 (back pain or backache or back ache).ti,ab,kw.

3 exp LOW BACK PAIN/

4 exp BACKACHE/

5 (lumb$ adj3 pain).ti,ab,kw.

6 coccyx.ti,ab,kw.

7 coccydynia.ti,ab,kw.

8 sciatica.ti,ab,kw.

9 sciatica/

10 exp ISCHIALGIA/

11 spondylosis.mp.

12 lumbago.ti,ab,kw.

13 back disorder$.ti,ab,kw.

14 or/1-13

15 systematic review /

16 meta-analysis /

17 (#15 OR #16)

18 (#14 AND #17)

Cochrane Database of Systematic Reviews

#1 MeSH descriptor: [Back Pain] explode all trees

#2 dorsalgia

#3 backache or back ache

#4 MeSH descriptor: [Back Pain] explode all trees

#5 lumb* near pain or coccyx or coccydynia or sciatica or spondylosis

#6 MeSH descriptor: [Spine] explode all trees

#7 MeSH descriptor: [Spinal Diseases] explode all trees

#8 lumbago or discitis or disc near herniat*

#9 spinal fusion

#10 facet near joint*

#11 MeSH descriptor: [Intervertebral Disk] explode all trees

#12 postlaminectomy

#13 arachnoiditis

#14 failed near back

#15 MeSH descriptor: [Cauda Equina] explode all trees

#16 lumb* near vertebra*

#17 spinal near stenosis

#18 slipped near (disc* or disk*)

#19 degenerat* near (disc* or disk*)

#20 stenosis near (spine or root or spinal)

#21 displace* near (disc* or disk*)

#22 prolap* near (disc* or disk*)

#23 MeSH descriptor: [Sciatic Neuropathy] explode all trees

#24 sciatic*

#25 back disorder*

#26 back near pain

#27 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26)

#28 systematic review

#29 meta-analysis

#30 (#28 or #29)

#31 (#27 AND #30)

PEDro

Problem: Pain

AND

Body Part: lumbar spine, sacro-iliac joint or pelvis

AND

Method: systematic review

CINAHL

S1 "lumbago"

S2 (MH "Spondylolisthesis") OR (MH "Spondylolysis")

S3 (MH "Thoracic Vertebrae")

S4 S1 or S2 or S3

S5 lumbar N2 vertebra

S6 (MH "Lumbar Vertebrae")

S7 "coccydynia"

S8 "coccyx"

S9 "sciatica"

S10 (MH "Sciatica")

S11 (MH "Coccyx")

S12 S5 or S6 or S7or S8 or S9 or S10 or S11

S13 backache or "back ache"

S14 lumb* W3 pain

S15 back pain

S16 (MH "Low Back Pain")

S17 (MH "Back Pain+")

S18 "dorsalgia"

S19 S13 S14 or S15 or S16 or S17 or S18 or S34

S20 S4 or S12 or S19

S21 systematic review

S22 meta-analysis

S23 S21 or S22

S24 S20 and S23

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al**:** Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X	☐	1-5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	X	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X	☐	54
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	☐	6-14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	☐	20-22
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	☐	X	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	X	☐	16-19
Sponsor	5b	Provide name for the review funder and/or sponsor	X	☐	16-19
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X	☐	16-19
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X	☐	79-131
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X	☐	133-137

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X	☐	147-159
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X	☐	160-167
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	X	☐	Appendix 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	☐	171-174
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X	☐	167-171
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