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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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Manuscripts

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3 1 THE INFLUENCE OF ALLOCATION CONCEALMENT AND INTENTION-
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5 2 TO-TREAT ANALYSIS ON TREATMENT EFFECTS OF PHYSICAL
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7 3 THERAPY INTERVENTIONS IN LOW BACK PAIN RANDOMIZED
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9 4 CONTROLLED TRIALS: A PROTOCOL OF A META-EPIDEMIOLOGICAL
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11 5 STUDY

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43 19 **AUTHORS' CONTRIBUTIONS**

45 20 MOA, BTS and LOPC conceived and designed the study. CM contributed to the
46
47 21 development of the protocol. All of the authors assisted in the final protocol and agreed
48
49 22 to its final approval before submission.

52 23 **COMPETING INTEREST**

54 24 None

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3 26 **ABSTRACT**

4 27 **Introduction:** The presence of methodological bias, such as inadequate allocation
5
6 28 concealment and lack of intention-to-treat analysis may overestimate the treatment
7
8 29 effects from randomized controlled trials. Meta-epidemiological studies have been
9
10 30 performed in a large number of health-care areas. However, there are no studies
11
12 31 investigating these issues in physical therapy interventions for patients with low back
13
14 32 pain. The aim of this study is to investigate the influence of allocation concealment and
15
16 33 the use of intention-to-treat analysis on estimates of the treatment effects of physical
17
18 34 therapy interventions in low back pain clinical trials from meta-analyses.

19
20 35 **Methods and analysis:** A search on PubMed, Embase, Cochrane Database of
21
22 36 Systematic Reviews and PEDro databases will be performed. We will include all meta-
23
24 37 analyses of randomized controlled trials that compared physical therapy interventions in
25
26 38 patients with low back pain compared with placebo or no intervention, and have pain
27
28 39 intensity or disability as the primary outcomes. Information about selection (allocation
29
30 40 concealment) and attrition bias (intention-to-treat analysis) will be extracted from the
31
32 41 PEDro Database. Information about bibliographic data, study characteristics,
33
34 42 participants' characteristics and study results will be extracted from each systematic
35
36 43 review. A random effect model of meta-analyses will be used to pool the effect sizes.
37
38 44 Finally, a meta-regression will be performed to assess the association between
39
40 45 methodological features (allocation concealment and intention to treat analysis) and
41
42 46 effect sizes. The dependent variable will be the effect size (the mean between-group
43
44 47 differences) for the primary outcomes (pain or disability), while the independent
45
46 48 variables will be the methodological features of interest (allocation concealment and
47
48 49 intention-to-treat analysis).

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2
3 50 **Ethics and dissemination:** No ethical approval required for this study. The study
4
5 51 findings will be published in a peer-reviewed journal and presented at
6
7 52 national/international conferences.

8
9
10 53 **Registration number:** PROSPERO (CRD42016052347).

11
12 54 **Keywords:** Epidemiologic Research Design; Low Back Pain; Physical Therapy
13
14 55 Modalities

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17
18 58 **Strengths and limitations of this study**

- 19
20
21 59 • This protocol was performed following the Preferred Reporting Items for
22
23 60 Systematic review and Meta-Analyses Protocols (PRISMA - P) guidelines.
- 24
25 61 • This study will be the first one to evaluate the association between
26
27 62 methodological characteristics and the treatment effects of physical therapy
28
29 63 interventions in low back pain trials.
- 30
31 64 • The results from this meta-epidemiological study are likely to bring new insights
32
33 65 to the physical therapy scientific community by informing issues that need to be
34
35 66 considered in randomized trials.

76 INTRODUCTION

77 Systematic reviews and meta-analyses of randomized controlled trials are
78 considered the ‘gold standard’ to evaluate the efficacy and effectiveness of healthcare
79 interventions.^{1,2} Despite systematic reviews and meta-analyses providing the best
80 available evidence to support clinical decision-making and to promote changes in health
81 policies, they are not free of bias.^{3,4} The presence of potential biases in clinical trials,
82 such as inadequate allocation concealment (selection bias) or lack of intention-to-treat
83 analysis (attrition bias) may overestimate the effect size of the interventions⁵⁻⁸. These
84 types of bias can directly influence the results from meta-analyses, leading to inaccurate
85 conclusions, misleading clinicians and researchers.⁹

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

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

1
2
3 100 allocation concealment were excluded.¹⁵ In contrast, the influence of performing ITT
4
5 101 analysis (or attrition bias) on the effect estimates of RCTs is still unclear.^{12,14,16}
6
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8 102 Most meta-epidemiological studies derived from reports of RCTs are from the
9
10 103 field of medicine. These studies are likely to be different from physical therapy trials,
11
12 104 especially regarding the type of intervention and outcomes assessed.¹⁷ To date, there is
13
14 105 only one meta-epidemiological study published that evaluated the relationship between
15
16 106 methodological characteristics and the treatment effects of physical therapy
17
18 107 interventions.¹⁷ This study included different areas of physical therapy and therefore,
19
20 108 selecting a wide range of different clinical conditions, leading to a large level of
21
22 109 heterogeneity that may hamper the association between the characteristics assessed and
23
24 110 treatment effects. Thus, we choose to focus on low back pain trials. Besides being the
25
26 111 most prevalent, costly and disabling musculoskeletal condition, low back pain is the
27
28 112 musculoskeletal condition with largest number of clinical trials in the literature.¹⁸⁻²⁰
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31
32 113 The lack of meta-epidemiological studies in the literature that have evaluated the
33
34 114 association between methodological characteristics and the treatment effects of
35
36 115 interventions in low back pain trials motivated us to conduct this study.
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40 117 **OBJECTIVES**

41
42 118 The objectives of this study are: (1) to establish if adequate allocation
43
44 119 concealment and the use of intention to treat analysis influence the effect size of
45
46 120 physical therapy interventions in meta-analyses of low back pain RCTs when compared
47
48 121 with meta-analyses of trials without these characteristics; (2) to evaluate if allocation
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50 122 concealment process and intention to treat analyses are evaluated and reported
51
52 123 adequately in clinical trials.
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3 125 **METHODS**

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5 126 **Study design**

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7 127 Protocol of a meta-epidemiological study

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9 128 **Protocol and registration**

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11 129 The protocol was prospectively registered at the International Prospective
12 Register of Systematic Reviews (PROSPERO), registration number: CRD42016052347.

13
14 130 We followed the Preferred Reporting Items for Systematic review and Meta-Analyses
15
16 131 Protocols (PRISMA - P)²¹ guidelines and the checklist is available (see appendix 1).

17
18 132
19
20 133 **Identification and selection of studies**

21
22 134 All meta-analyses of randomized controlled trials evaluating treatment of non-
23
24 135 specific low back pain will be included in this study. Non-specific low back pain is
25
26 136 defined as low back pain not attributed to a specific pathology, such as nerve root
27
28 137 compromise or serious spinal pathology.²² We will include meta-analyses composed of
29
30 138 RCTs comparing physical therapy interventions in adult patients with non-specific low
31
32 139 back pain with placebo or no intervention, and have pain intensity measured by
33
34 140 continuous measures (such as the 11-point numerical rating scale) or disability (such as
35
36 141 the Rolland-Morris Disability Questionnaire or Oswestry Disability Index) as the main
37
38 142 outcomes. Any meta-analysis with mixed populations will be excluded. Overview of
39
40 143 reviews will also not be included in our study. In the case of Cochrane reviews, if there
41
42 144 are multiple versions of the same review (i.e., updates), we will include only the most
43
44 145 recent one.

45
46 146 Identification of studies to be included will be done through an electronic search
47
48 147 without language restriction and publication date in the following databases: PubMed
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50 148 (<https://www.ncbi.nlm.nih.gov/pubmed>), Embase via OvidSP, Cochrane Database of
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52 149 Systematic Reviews (<http://www.cochranelibrary.com/>) and PEDro
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1
2
3 150 (<http://pedro.org.au/>). The search strategy will combine validated filters related to meta-
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5 151 analyses and systematic reviews with physical therapy interventions on low back pain
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7 152 (See appendix 2 for more details). Two review authors will independently assess and
8
9 153 select potential studies to be included based on titles and abstracts. Any discordance
10
11 154 will be solved by consensus, and if necessary, a third evaluator will arbitrate the final
12
13 155 decision. Full-texts of selected articles will be collected and evaluated in the same
14
15 156 manner.

17 157 **Risk of bias assessment (selection and attrition bias)**

18
19 158 We will extract the information about selection (allocation concealment) and
20
21 159 attrition bias (use of intention to treat analysis) from the Physiotherapy Evidence
22
23 160 Database (PEDro) for each RCT.²³ The definitions used by the PEDro database about
24
25 161 these domains are: *allocation concealment process is considered adequate, if the*
26
27 162 *responsible for assignment has no information about participants included in the trial*
28
29 163 *and has no influence on the assignment sequence or on the decision about eligibility of*
30
31 164 *the participant (such as, use of sequentially sealed opaque envelopes or “off-site”*
32
33 165 *allocation); ITT analysis means that all participants were analyzed in the groups to*
34
35 166 *which they were originally allocated.*²³ When the score of domain bias from an included
36
37 167 article is not available at PEDro database, two review authors will independently assess
38
39 168 it, following the same recommendations stated above. Any disagreements will be
40
41 169 resolved by discussion or arbitration by a third reviewer when consensus cannot be
42
43 170 reached.

44 171 **Data extraction and synthesis**

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46 172 Two review authors will independently extract data from selected systematic
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48 173 reviews using a standardized extraction form. Any discordance will also be resolved by
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50 174 discussion or arbitration by a third reviewer when consensus cannot be reached.
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3 175 We will extract bibliographic data (authors, title and year of publication), study
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5 176 characteristics (design, sample size and intervention used), characteristics of the
6
7 177 participants (gender, age, duration and severity of the condition), results of studies
8
9 178 included in the meta-analysis (mean and standard deviation). We will only extract
10
11 179 outcomes from the short-term follow-up (closest to 4 weeks). E-mail requests will be
12
13 180 sent to trial authors for additional information data, when necessary.

16 181 **Data analysis and synthesis**

17
18 182 In order to determine whether allocation concealment and ITT analysis affect
19
20 183 treatment effect of interventions, a two-level analysis will be conducted. Initially, the
21
22 184 effect size of each study will be calculated by dividing the mean difference between
23
24 185 groups by the standard deviation values.²⁴ A negative effect size indicates a beneficial
25
26 186 effect of the experimental intervention. Individual study data will be retrieved from the
27
28 187 meta-analyses included in our study.

29
30 188 After that, we will calculate two pooled effect size for each meta-analysis by
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32 189 using a random effect model: one corresponding to the pooled effect size from studies
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34 190 with the characteristics of interest (allocation concealment and ITT analysis) and the
35
36 191 other for studies without these characteristics. A negative difference in effect size
37
38 192 indicates a beneficial effect of studies without the characteristics of interest for the
39
40 193 experimental group. We will assess between-trial heterogeneity using I-squared test (I^2).
41
42 194 This test demonstrates whether the percentage of total variation across studies is
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44 195 explained by heterogeneity rather than chance. An I^2 higher than 75% will be
45
46 196 considered as 'high heterogeneity', an I^2 of 50% to 75% will be considered as 'moderate
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48 197 heterogeneity', and an I^2 lower than 25% will be considered as 'low heterogeneity'.²⁵
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50 198 Review Manager (RevMan) version 5 software will be used for all meta-analyses and
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52 199 heterogeneity assessment.
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3 200 The second-level analysis will be a meta-regression to evaluate the association
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5 201 between characteristics of included studies and effect size. The dependent variable will
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7 202 the effect size (mean between-group difference) for the main outcomes (pain or
8
9 203 disability), while the independent variables will be the methodological characteristics of
10
11 204 interest (allocation concealment and ITT analysis). Additionally, we will use three
12
13
14 205 independent covariates in meta-regression analysis: sample size, sequence generation
15
16 206 and heterogeneity. The sample size will be classified as 'small' (< 100 patients
17
18 207 randomized per arm) or 'high' (\geq 100 patients randomized per arm).²⁶ Sequence
19
20 208 generation is considered adequate when subjects were randomly allocated to groups
21
22 209 (e.g., computer-generated random numbers; coin-tossing and dice-rolling).²³ For the
23
24 210 heterogeneity assessment, we will adopt the classification described above. The
25
26 211 covariates will be used according to the number of studies included. For each 10 trials,
27
28 212 one covariate will be incorporated to the analysis. Random-effects meta-regression will
29
30 213 be conducted using the 'metareg' command in STATA 10 and weighted using effect
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32 214 size standard errors.
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38 216 **DISCUSSION**

39
40 217 To our knowledge, this is the first study aimed to investigate if meta-analyses'
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42 218 findings and the magnitude of the effect sizes of physical therapy intervention in low
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44 219 back pain RCTs could be influenced by methodological features (i.e., allocation
45
46 220 concealment and ITT analysis). Meta-analyses from RCTs are responsible for the most
47
48 221 reliable evidence on the treatment of patients with low-back pain, and its results are of
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50 222 interest to a range of stakeholders. However, biased results from RCTs can lead to
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52 223 inadequate clinical decision making and consequently affect patient outcomes.
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3 224 Therefore, we believe that the findings of this meta-epidemiological study will
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5 225 provide important contributions to clinicians, researchers, and policy-makers in the low-
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7 226 back pain field. This study will improve the available evidence for physical therapists,
8
9 227 through the disclosure of reliable and unbiased results on clinical decision-making. It
10
11 228 will also help promoting better politics of evidence-based in this area by detecting
12
13 229 possible issues while interpreting trials of physical therapy interventions for patients
14
15 230 with back pain.

16
17
18 231 The present meta-epidemiological study has some strength points. Since this
19
20 232 approach is such similar to a systematic review, we will approach strictly methods to
21
22 233 identify and select studies to be included through defined inclusion criteria and sensitive
23
24 234 search strategy. Data extraction and analysis will be also performed by rigorous
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26 235 methods to avoid potential bias in this study.

27
28
29 236 The limitation of the present study is the fact that it is restricted to meta-analyses
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31 237 of physical therapy interventions in non-specific low back pain. Thus, our results may
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33 238 have limited generalizability to other interventions as well as other clinical conditions.

34 239 **Dissemination**

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36
37 240 We intend to disseminate our results through presentations at national and
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39 241 international conferences (e.g., World Confederation for Physical Therapy and
40
41 242 International Back and Neck Pain Forum) as well as publishing our study in a high-
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43 243 impact international scientific journal.

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48 245 **COMPETING INTEREST**

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51 246 None

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55 248 **REFERENCES**

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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.

- 1
2
3 3 exp LOW BACK PAIN/
4
5 4 exp BACKACHE/
6
7 5 (lumb\$ adj3 pain).ti,ab,kw.
8
9
10 6 coccyx.ti,ab,kw.
11
12 7 coccydynia.ti,ab,kw.
13
14 8 sciatica.ti,ab,kw.
15
16 9 sciatica/
17
18 10 exp ISCHIALGIA/
19
20
21 11 spondylosis.mp.
22
23 12 lumbago.ti,ab,kw.
24
25 13 back disorder\$.ti,ab,kw.
26
27 14 or/1-13
28
29 15 systematic review /
30
31 16 meta-analysis /
32
33 17 (#15 OR #16)
34
35 18 (#14 AND #17)
36
37
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41 **Cochrane Database of Systematic Reviews**

- 42
43 #1 MeSH descriptor: [Back Pain] explode all trees
44
45 #2 dorsalgia
46
47 #3 backache or back ache
48
49 #4 MeSH descriptor: [Back Pain] explode all trees
50
51 #5 lumb* near pain or coccyx or coccydynia or sciatica or spondylosis
52
53 #6 MeSH descriptor: [Spine] explode all trees
54
55 #7 MeSH descriptor: [Spinal Diseases] explode all trees
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- 1
2
3 #8 lumbago or discitis or disc near herniat*
4
5 #9 spinal fusion
6
7 #10 facet near joint*
8
9 #11 MeSH descriptor: [Intervertebral Disk] explode all trees
10
11 #12 postlaminectomy
12
13 #13 arachnoiditis
14
15 #14 failed near back
16
17 #15 MeSH descriptor: [Cauda Equina] explode all trees
18
19 #16 lumb* near vertebra*
20
21 #17 spinal near stenosis
22
23 #18 slipped near (disc* or disk*)
24
25 #19 degenerat* near (disc* or disk*)
26
27 #20 stenosis near (spine or root or spinal)
28
29 #21 displace* near (disc* or disk*)
30
31 #22 prolap* near (disc* or disk*)
32
33 #23 MeSH descriptor: [Sciatic Neuropathy] explode all trees
34
35 #24 sciatic*
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37 #25 back disorder*
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39 #26 back near pain
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41 #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
42 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or
43 #26)
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45 #28 systematic review
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47 #29 meta-analysis
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49 #30 (#28 or #29)
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51 #31 (#27 AND #30)
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PEDro

Problem: Pain

AND

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

AND

Method: systematic review

For peer review only

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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	53
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6-14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n/a
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n/a
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	16-18
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	76-115
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	Appendix 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	157-170
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	<input type="checkbox"/>	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	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	210-214
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n/a
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n/a
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	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

Journal:	<i>BMJ Open</i>
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Primary Subject Heading:	Research methods
Secondary Subject Heading:	Research methods, Evidence based practice, Rehabilitation medicine
Keywords:	Epidemiologic Research Design, Low Back Pain, Physical Therapy Modalities

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Manuscripts

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3 1 THE INFLUENCE OF ALLOCATION CONCEALMENT AND INTENTION-
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5 2 TO-TREAT ANALYSIS ON TREATMENT EFFECTS OF PHYSICAL
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7 3 THERAPY INTERVENTIONS IN LOW BACK PAIN RANDOMISED
8
9 4 CONTROLLED TRIALS: A PROTOCOL OF A META-EPIDEMIOLOGICAL
10
11 5 STUDY

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15
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36 16 **FUNDING STATEMENT**

38 17 Matheus Almeida is supported by São Paulo Research Foundation (FAPESP) -
39
40 18 grant #2016/10317-0. The funder had no role in the design of the study and will not be
41
42 19 involved in the interpretation or publication of the results.

45 20 **AUTHORS' CONTRIBUTIONS**

47 21 MOA, BTS, CM and LOPC conceived and designed the study. All of the authors
48
49 22 assisted in the final protocol and agreed to its final approval before submission.

52 23 **COMPETING INTEREST**

54 24 None

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2
3 26 **ABSTRACT**

4 27 **Introduction:** Meta-epidemiological studies examining the influence of methodological
5
6
7 28 such as inadequate allocation concealment and lack of intention-to-treat analysis
8
9 29 features have been performed in a large number of health-care areas. However, there are
10
11 30 no studies investigating these biases in physical therapy interventions for patients with
12
13 31 low back pain. The aim of this study is to investigate the influence of allocation
14
15 32 concealment and the use of intention-to-treat analysis on estimates of the treatment
16
17 33 effects of physical therapy interventions in low back pain clinical trials.

18
19
20 34 **Methods and analysis:** Searches on PubMed, Embase, Cochrane Database of
21
22 35 Systematic Reviews, PEDro and CINAHL databases will be performed. We will search
23
24 36 for systematic reviews that include a meta-analysis of randomised controlled trials that
25
26 37 compared physical therapy interventions in patients with low back pain compared with
27
28 38 placebo or no intervention, and have pain intensity or disability as the primary
29
30 39 outcomes. Information about selection (allocation concealment) and attrition bias
31
32 40 (intention-to-treat analysis) will be extracted from the PEDro Database for each
33
34 41 included trial. Information about bibliographic data, study characteristics, participants'
35
36 42 characteristics and study results will be extracted. A random effects model of meta-
37
38 43 analyses will be used to pool the treatment effects comparing trials with allocation
39
40 44 concealment and intention-to-treat analysis with those that did not include these
41
42 45 features. A meta-regression will be performed to measure the association between
43
44 46 methodological features and treatment effects considering each trial. The dependent
45
46 47 variable will be the treatment effects (the mean between-group differences) for the
47
48 48 primary outcomes (pain or disability), while the independent variables will be the
49
50 49 methodological features of interest (allocation concealment and intention-to-treat
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52 50 analysis). Other covariates will include sample size and sequence generation.
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3 51 **Ethics and dissemination:** No ethical approval will be required for this study. The
4
5 52 study findings will be published in a peer-reviewed journal and presented at
6
7 53 international conferences.

8
9 54 **Registration number:** PROSPERO (CRD42016052347).

10
11 55 **Keywords:** Epidemiologic Research Design; Low Back Pain; Physical Therapy
12
13 56 Modalities

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19 59 **Strengths and limitations of this study**

- 20
21 60 • This protocol was specified following the Preferred Reporting Items for
22
23 61 Systematic review and Meta-Analyses Protocols (PRISMA - P) guidelines.
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25 62 • This study will be the first one to evaluate the association between
26
27 63 methodological characteristics and the treatment effects of physical therapy
28
29 64 interventions in low back pain trials.
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31 65 • The results from this meta-epidemiological study are likely to bring new insights
32
33 66 to the physical therapy scientific community by informing issues that need to be
34
35 67 considered in randomised trials.
36
37 68 • The findings from this meta-epidemiological study may have limited
38
39 69 generalisability to other clinical conditions, since it is restricted to physical
40
41 70 therapy treatment of low back pain.
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78 INTRODUCTION

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

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

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

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2
3 102 allocation concealment were excluded.¹⁵ In contrast, the influence of performing ITT
4
5 103 analysis (or attrition bias) on the effect estimates of RCTs is still unclear.^{12,14,16}
6

7 104 Most meta-epidemiological studies derived from reports of RCTs are from the
8
9 105 field of medicine. These studies are likely to be different from physical therapy trials,
10
11 106 especially regarding the type of intervention and outcomes assessed.¹⁷ To date, there is
12
13 107 only one meta-epidemiological study published that evaluated the relationship between
14
15 108 methodological characteristics and the treatment effects of physical therapy
16
17 109 interventions.¹⁷ This study included different areas of physical therapy and therefore,
18
19 110 selecting a wide range of different clinical conditions, leading to a large level of
20
21 111 heterogeneity that may hamper the association between the characteristics assessed and
22
23 112 treatment effects. Therefore, we chose to focus on low back pain trials. Besides being
24
25 113 the most prevalent, costly and disabling musculoskeletal condition, low back pain is the
26
27 114 musculoskeletal condition with largest number of clinical trials in the physiotherapy
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29 115 literature.¹⁸⁻²¹
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34 116 The lack of meta-epidemiological studies that have evaluated the association
35
36 117 between methodological characteristics and the treatment effects of interventions in low
37
38 118 back pain trials motivated us to conduct this study.
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42 120 **OBJECTIVES**

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45 121 The objectives of this study are: (1) to establish if adequate allocation
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47 122 concealment and the use of intention to treat analysis influence the treatment effects of
48
49 123 physical therapy interventions in systematic reviews with meta-analysis of low back
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51 124 pain RCTs when compared with systematic reviews with meta-analysis of trials without
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53 125 these characteristics; (2) to evaluate if allocation concealment and intention to treat
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55 126 analyses are evaluated and reported adequately in clinical trials.
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5 128 **METHODS**

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7 129 **Study design**

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10 130 This is a protocol of a meta-epidemiological study.

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12 131 **Protocol and registration**

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14 132 The protocol was prospectively registered at the International Prospective
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16 133 Register of Systematic Reviews (PROSPERO), registration number: CRD42016052347.
17
18 134 We followed the Preferred Reporting Items for Systematic review and Meta-Analyses
19
20 135 Protocols (PRISMA - P)²² guidelines and the checklist is available (see appendix 1).

21
22 136 **Identification and selection of studies**

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25 137 All RCTs included in systematic reviews with meta-analysis evaluating physical
26
27 138 therapy treatment in adults with non-specific low back pain that included pain or
28
29 139 disability (as continuous variables) as the main outcomes will be included in this study.
30
31 140 Non-specific low back pain is defined as low back pain not attributed to a specific
32
33 141 pathology, such as nerve root compromise or serious spinal pathology.²³ The physical
34
35 142 therapy intervention will be compared with placebo or no intervention. We will consider
36
37 143 all possible meta-analyses from the same systematic review, since a systematic review
38
39 144 may contain more than one meta-analysis (e.g different outcomes). Any systematic
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41 145 reviews with meta-analysis with mixed populations will not be considered. Overview of
42
43 146 reviews will also not be considered in our study. In the case of Cochrane reviews, if
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45 147 there are multiple versions of the same review (i.e., updates), we will consider only the
46
47 148 most recent one.

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50 149 Potentially eligible studies to be included will be retrieved through an electronic
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52 150 search in the following databases from their inception up to February 2017: PubMed
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54 151 (<https://www.ncbi.nlm.nih.gov/pubmed>), Embase via OvidSP, Cochrane Database of
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3 152 Systematic Reviews (<http://www.cochranelibrary.com/>), PEDro (<http://pedro.org.au/>)
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5 153 and CINAHL (<https://health.ebsco.com/products/the-cinahl-database>). There will be no
6
7 154 restriction to language of studies. The search strategy will combine validated filters
8
9 155 related to systematic reviews and meta-analyses with physical therapy interventions on
10
11 156 low back pain (See appendix 2 for more details). Two review authors will
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13 157 independently assess and select potential studies to be included based on titles and
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15 158 abstracts. Any discordance will be solved by consensus, and if necessary, a third
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17 159 evaluator will arbitrate the final decision. Full-texts of selected articles will be collected
18
19 160 and evaluated in the same manner. After the process of identification and selection, we
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21 161 will retrieve the full-texts to extract the data. Two authors from our study are raters of
22
23 162 the PEDro database, so it will be possible to obtain the full texts that are indexed on this
24
25 163 database. It is important to state that about 92% of physical therapy RCTs are indexed
26
27 164 on the PEDro database.²⁴ For those RCTs not indexed on PEDro, we will make all
28
29 165 efforts to get these full texts (searching other databases, contact authors).
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36 167 **Risk of bias assessment (selection and attrition bias)**

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38 168 We will extract the information about selection (allocation concealment) and
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40 169 attrition bias (intention to treat analysis) from the Physiotherapy Evidence Database
41
42 170 (PEDro) for all trials included in the systematic reviews.²⁵ We decided to use the PEDro
43
44 171 scale due to the following reasons: 1) the PEDro scale has high reliability for individual
45
46 172 ratings and consensus ratings and can be used as a continuous scale for measuring the
47
48 173 methodological quality of trials;^{25,26} 2) the PEDro scale is strongly correlated ($r=0.83$;
49
50 174 95% CI 0.76 to 0.88) with the Cochrane Risk of Bias tool;²⁷ and 3) Feasibility: as two
51
52 175 authors from this study are raters from the PEDro database, we can easily download the
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54 176 PEDro scores for the included RCTs in our study. The definitions used by the PEDro
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3 177 database about these domains are: *allocation concealment process is considered*
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5 178 *adequate, if the responsible for assignment has no information about participants*
6
7 179 *included in the trial and has no influence on the assignment sequence or on the decision*
8
9 180 *about eligibility of the participant (such as, use of sequentially sealed opaque envelopes*
10
11 181 *or “off-site” allocation); ITT analysis means that all participants were analyzed in the*
12
13 182 *groups to which they were originally allocated.*²⁵ Each domain will be rated as ‘yes’,
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15 183 when the criterion is clearly satisfied, or ‘no’ when the criterion is not satisfied or the
16
17 184 information is unclear in the text. When the score of domain bias from an included
18
19 185 article is not available at the PEDro database (the article may not be indexed in PEDro
20
21 186 database; or the article may be in process to be rated), two assessors, not involved in the
22
23 187 study, will independently assess it, following the same recommendations stated above.
24
25 188 Any disagreements will be resolved by discussion or arbitration by a third assessor
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27 189 when consensus cannot be reached. The assessors are trained raters of the PEDro scale
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29 190 that work in our department and will be blinded to the scope of the manuscript.
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34 191 **Data extraction and synthesis**

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36 192 Two review authors will independently extract data from all trials included in
37
38 193 the selected systematic reviews using a standardized extraction form. Any discordance
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40 194 will also be resolved by discussion or arbitration by a third reviewer when consensus
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42 195 cannot be reached.
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45 196 We will extract bibliographic data (authors, title and year of publication), study
46
47 197 characteristics (design, sample size and intervention used), characteristics of the
48
49 198 participants (gender, age, duration and severity of the condition), outcomes results
50
51 199 (mean and standard deviation). We will only extract outcomes results from the short-
52
53 200 term follow-up (closest to 4 weeks). E-mail requests will be sent to trial authors for
54
55 201 additional information data, when necessary.
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202 Data analysis and synthesis

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

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

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

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3 227 The second stage of the analysis will be a meta-regression to evaluate the
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5 228 association between methodological characteristics of included trials and the treatment
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7 229 effects.¹¹ The dependent variable will be the treatment effects (mean between-group
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9 230 difference) for the main outcomes (pain or disability), while the independent variables
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11 231 will be the methodological characteristics of interest (allocation concealment and ITT
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13 232 analysis). Additionally, we will use two independent covariates in meta-regression
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15 233 analysis: sample size and sequence generation. We decided to investigate the effect of
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17 234 sequence generation and sample size since these variables have been associated with
18
19 235 treatment effect estimates.³¹ Sequence generation assessment is considered adequate
20
21 236 when subjects were randomly allocated to groups (e.g., computer-generated random
22
23 237 numbers; coin-tossing and dice-rolling).²⁵ The sample size will be considered as a
24
25 238 continuous quantitative variable in the meta-regression model. The covariates will be
26
27 239 used according to the number of studies included. For each 10 trials, one covariate will
28
29 240 be incorporated to the analysis. Random-effects meta-regression will be conducted
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31 241 using the ‘metareg’ command in STATA 10 and weighted using effect size standard
32
33 242 errors.¹¹
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244 **DISCUSSION**

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

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3 251 However, biased results from RCTs can lead to inadequate clinical decision-
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5 252 making and consequently affect patient outcomes. Clinicians may select interventions
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7 253 for their patients based on trials results that are inflated, and so these are not a very
8
9 254 reliable guide to treatment selection. For example, a systematic review about the
10
11 255 effectiveness of low level laser therapy for chronic LBP found a significantly greater
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13 256 reduction in pain in response to laser therapy compared to placebo.³² However, this
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15 257 finding was based on a meta-analysis with three clinical trials that did not conceal
16
17 258 allocation or use an ITT analysis, so this result could be an overestimate of the true
18
19 259 effect of laser. If this premise of overestimated effect is true, clinicians might in good
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21 260 faith select interventions that might not help their patients.
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25 261 Therefore, we believe that the findings of this meta-epidemiological study will
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27 262 provide important contributions to clinicians, researchers, and policy-makers in the low-
28
29 263 back pain field. This study will improve the available evidence for physical therapists,
30
31 264 through the disclosure of reliable and unbiased results on clinical decision-making. It
32
33 265 will also help promoting better politics of evidence-based in this area by detecting
34
35 266 possible issues while interpreting trials of physical therapy interventions for patients
36
37 267 with back pain.
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41 268 The present meta-epidemiological study has a number of strengths. Since this
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43 269 approach is similar to a systematic review, we will pre-specify methods to identify and
44
45 270 select studies to be included through pre-defined inclusion criteria and sensitive search
46
47 271 strategy. Data extraction and analysis will be also performed by rigorous methods to
48
49 272 avoid potential bias in this study.
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51
52 273 The limitation of the present study is the fact that it is restricted to meta-analyses
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54 274 of physical therapy interventions in non-specific low back pain. Thus, our results may
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3 275 have limited generalizability to other interventions as well as to other clinical
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5 276 conditions.

7 277 **Dissemination**

9 278 We intend to disseminate our results through presentations at national and
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11 279 international conferences (e.g., World Confederation for Physical Therapy and
12
13 280 International Back and Neck Pain Forum) as well as publishing our study in a high-
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15 281 impact international scientific journal.
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21 283 **COMPETING INTEREST**

22
23 284 None
24
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26

27 286 **REFERENCES**

- 28
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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	<input type="checkbox"/>	1-5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	X	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X	<input type="checkbox"/>	57
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	<input type="checkbox"/>	6-14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	<input type="checkbox"/>	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	<input type="checkbox"/>	X	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	X	<input type="checkbox"/>	16-19
Sponsor	5b	Provide name for the review funder and/or sponsor	X	<input type="checkbox"/>	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	<input type="checkbox"/>	16-19
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	Appendix 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	168-191
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	<input type="checkbox"/>	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	<input type="checkbox"/>	212-227
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X	<input type="checkbox"/>	228-243
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	X	n/a
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective	<input type="checkbox"/>	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)	<input type="checkbox"/>	X	n/a

For peer review only

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.

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3 3 exp LOW BACK PAIN/
4
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6 4 exp BACKACHE/
7
8 5 (lumb\$ adj3 pain).ti,ab,kw.
9
10 6 coccyx.ti,ab,kw.
11
12 7 coccydynia.ti,ab,kw.
13
14
15 8 sciatica.ti,ab,kw.
16
17 9 sciatica/
18
19 10 exp ISCHIALGIA/
20
21 11 spondylosis.mp.
22
23 12 lumbago.ti,ab,kw.
24
25 13 back disorder\$.ti,ab,kw.
26
27 14 or/1-13
28
29 15 systematic review /
30
31 16 meta-analysis /
32
33 17 (#15 OR #16)
34
35 18 (#14 AND #17)
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44 **Cochrane Database of Systematic Reviews**

45
46 #1 MeSH descriptor: [Back Pain] explode all trees

47
48 #2 dorsalgia

49
50 #3 backache or back ache

51
52 #4 MeSH descriptor: [Back Pain] explode all trees

53
54 #5 lumb* near pain or coccyx or coccydynia or sciatica or spondylosis

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56 #6 MeSH descriptor: [Spine] explode all trees

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58 #7 MeSH descriptor: [Spinal Diseases] explode all trees
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3 #8 lumbago or discitis or disc near herniat*
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6 #9 spinal fusion
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8 #10 facet near joint*
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10 #11 MeSH descriptor: [Intervertebral Disk] explode all trees
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12 #12 postlaminectomy
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15 #13 arachnoiditis
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18 #14 failed near back
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20 #15 MeSH descriptor: [Cauda Equina] explode all trees
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22 #16 lumb* near vertebra*
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25 #17 spinal near stenosis
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27 #18 slipped near (disc* or disk*)
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29 #19 degenerat* near (disc* or disk*)
30
31 #20 stenosis near (spine or root or spinal)
32
33 #21 displace* near (disc* or disk*)
34
35 #22 prolap* near (disc* or disk*)
36
37
38 #23 MeSH descriptor: [Sciatic Neuropathy] explode all trees
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41 #24 sciatic*
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43
44 #25 back disorder*
45
46 #26 back near pain
47
48 #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
49 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or
50 #26)
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52
53 #28 systematic review
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55 #29 meta-analysis
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57
58 #30 (#28 or #29)
59
60 #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 S7 or 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+")

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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

For peer review only

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

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			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	57
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6-14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	16-19
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	16-19
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	16-19
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	79-119
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	Appendix 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	168-191
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	<input type="checkbox"/>	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	<input type="checkbox"/>	212-227
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	X	<input type="checkbox"/>	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	<input type="checkbox"/>	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)	<input type="checkbox"/>	X	n/a
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	X	n/a

peer review only

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017301.R2
Article Type:	Protocol
Date Submitted by the Author:	01-Aug-2017
Complete List of Authors:	Almeida, Matheus; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy; Saragiotto, Bruno; The University of Sydney, School of Public Health, Sydney Medical School Maher, Chris; The University of Sydney, School of Public Health, Sydney Medical School Costa, Leonardo; Universidade Cidade de Sao Paulo, Masters and Doctoral Programs in Physical Therapy
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Research methods, Evidence based practice, Rehabilitation medicine
Keywords:	Epidemiologic Research Design, Low Back Pain, Physical Therapy Modalities

SCHOLARONE™
Manuscripts

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3 1 THE INFLUENCE OF ALLOCATION CONCEALMENT AND INTENTION-
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5 2 TO-TREAT ANALYSIS ON TREATMENT EFFECTS OF PHYSICAL
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7 3 THERAPY INTERVENTIONS IN LOW BACK PAIN RANDOMIZED
8
9 4 CONTROLLED TRIALS: A PROTOCOL OF A META-EPIDEMIOLOGICAL
10
11 5 STUDY

14 6 Matheus Oliveira de Almeida¹, Bruno T Saragiotto², Chris G Maher², Leonardo
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36 16 **FUNDING STATEMENT**

38 17 Matheus Almeida is supported by São Paulo Research Foundation (FAPESP) -
39
40 18 grant #2016/10317-0. The funder had no role in the design of the study and will not be
41
42 19 involved in the interpretation or publication of the results.

45 20 **AUTHORS' CONTRIBUTIONS**

47 21 MOA, BTS, CM and LOPC conceived and designed the study. All authors
48
49 22 reviewed the final protocol and agreed to its final approval before submission.

52 23 **COMPETING INTEREST**

54 24 None

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2
3 26 **ABSTRACT**

4 27 **Introduction:** Meta-epidemiological studies examining the influence of methodological
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6 28 characteristics, such as allocation concealment and intention-to-treat analysis have been
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8
9 29 performed in a large number of health-care areas. However, there are no studies
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11 30 investigating these characteristics in physical therapy interventions for patients with low
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13 31 back pain. The aim of this study is to investigate the influence of allocation concealment
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15 32 and the use of intention-to-treat analysis on estimates of treatment effects of physical
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17 33 therapy interventions in low back pain clinical trials.

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20 34 **Methods and analysis:** Searches on PubMed, Embase, Cochrane Database of
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22 35 Systematic Reviews, PEDro and CINAHL databases will be performed. We will search
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24 36 for systematic reviews that include a meta-analysis of randomized controlled trials that
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26 37 compared physical therapy interventions in patients with low back pain with placebo or
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28 38 no intervention, and have pain intensity or disability as the primary outcomes.
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30 39 Information about selection (allocation concealment) and attrition bias (intention-to-
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32 40 treat analysis) will be extracted from the PEDro Database for each included trial.
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34 41 Information about bibliographic data, study characteristics, participants' characteristics
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36 42 and study results will be extracted. A random effects model will be used to provide
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38 43 separate estimates of treatment effects for trials with and without allocation
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40 44 concealment and with and without intention to treat analysis (e.g., four estimates). A
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42 45 meta-regression will be performed to measure the association between methodological
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44 46 features and treatment effects from each trial. The dependent variable will be the
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46 47 treatment effect (the mean between-group differences) for the primary outcomes (pain
47
48 48 or disability), while the independent variables will be the methodological features of
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50 49 interest (allocation concealment and intention-to-treat analysis). Other covariates will
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52 50 include sample size and sequence generation.
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3 51 **Ethics and dissemination:** No ethical approval will be required for this study. The
4
5 52 study findings will be published in a peer-reviewed journal and presented at
6
7 53 international conferences.

8
9 54 **Registration number:** PROSPERO (CRD42016052347).

10
11 55 **Keywords:** Epidemiologic Research Design; Low Back Pain; Physical Therapy
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13 56 Modalities

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19 59 **Strengths and limitations of this study**

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21 60 • This protocol was specified following the Preferred Reporting Items for
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23 61 Systematic review and Meta-Analyses Protocols (PRISMA - P) guidelines.
24
25 62 • This study will be the first to evaluate the association between methodological
26
27 63 characteristics and estimates of the treatment effects of physical therapy
28
29 64 interventions in low back pain trials.
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31 65 • The results from this meta-epidemiological study are likely to bring new insights
32
33 66 to the physical therapy scientific community by informing issues that need to be
34
35 67 considered in randomized trials.
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37 68 • The findings from this meta-epidemiological study may have limited
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39 69 generalizability to other clinical conditions, since it is restricted to physical
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41 70 therapy treatment of low back pain.
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78 INTRODUCTION

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

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

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

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3 103 deviated from ITT.¹⁷ However, the influence of performing ITT analysis on the effect
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5 104 estimates of RCTs is still unclear.^{13,14,18} The direction and magnitude of the influence of
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7 105 performing ITT analysis may vary between studies according to different methods and
8
9 106 definitions used. For example, Dossing et al¹⁹ classified trials as ITT analysis or
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11 107 ‘modified ITT’ analysis. They classified trials as using an ITT analysis if all
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13 108 randomized patients were included in analysis, including both patients with clinical
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15 109 outcome data and patients with imputed outcome data; and ‘modified ITT’ analysis if
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17 110 some individuals were excluded from the analyses despite the authors of the trial
18
19 111 referring to it as being ITT. No significant difference in the treatment effect was found
20
21 112 between trials that performed ITT analysis compared to ‘modified ITT’ analysis. In
22
23 113 contrast, Abraha et al²⁰, using a different definition for deviation from ITT analysis
24
25 114 without taking into account the occurrence of post-randomization exclusions, found that
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27 115 the treatment effect of trials that performed ‘modified ITT’ analysis was inflated by
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29 116 17% compared to trials that performed ITT analysis.
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34 117 Most meta-epidemiological studies derived from reports of RCTs are from the
35
36 118 field of medicine. These studies are likely to be different from physical therapy trials,
37
38 119 especially regarding the type of intervention and outcomes assessed.²¹ To date, there is
39
40 120 only one meta-epidemiological study published that evaluated the relationship between
41
42 121 methodological characteristics and estimates of treatment effect of physical therapy
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44 122 interventions.²¹ This study included different areas of physical therapy and therefore,
45
46 123 selecting a wide range of different clinical conditions, leading to a large level of
47
48 124 heterogeneity that may hamper the association between the characteristics assessed and
49
50 125 treatment effects. Therefore, we chose to focus on low back pain trials. Besides being
51
52 126 the most prevalent, costly and disabling musculoskeletal condition, low back pain is the
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3 127 musculoskeletal condition with largest number of clinical trials in the physical therapy
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5 128 literature.²²⁻²⁵
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8 129 The lack of meta-epidemiological studies that have evaluated the association
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10 130 between methodological characteristics and the treatment effects of interventions in low
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12 131 back pain trials motivated us to conduct this study.
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133 **OBJECTIVES**

134 The objectives of this study are: (1) to establish if adequate allocation
135 concealment and the use of ITT analysis influence the estimates of treatment effect of
136 physical therapy interventions in low back pain RCTs and (2) to evaluate if allocation
137 concealment and ITT analysis are evaluated and reported adequately in clinical trials.
138

139

139 **METHODS**

140 **Study design**

141 This is a protocol of a meta-epidemiological study.

142 **Protocol and registration**

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

147 **Identification and selection of studies**

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

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3 152 pathology, such as nerve root compromise or serious spinal pathology.²⁷ The physical
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5 153 therapy intervention will be compared with placebo or no intervention. We will consider
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7 154 all possible meta-analyses from the same systematic review, since a systematic review
8
9 155 may contain more than one meta-analysis (e.g. different outcomes). Meta-analyses with
10
11 156 only one trial will be excluded. Any systematic reviews with meta-analysis with mixed
12
13 157 populations will not be considered. Overview of reviews will also not be considered in
14
15 158 our study. In the case of Cochrane reviews, if there are multiple versions of the same
16
17 159 review (e.g., updates), we will consider only the most recent one.

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21 160 Potentially eligible systematic reviews to be included will be retrieved through
22
23 161 an electronic search in the following databases from their inception up to February
24
25 162 2017: PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>), Embase via OvidSP, Cochrane
26
27 163 Database of Systematic Reviews (<http://www.cochranelibrary.com/>), PEDro
28
29 164 (<http://pedro.org.au/>) and CINAHL ([https://health.ebsco.com/products/the-cinahl-](https://health.ebsco.com/products/the-cinahl-database)
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31 165 [database](https://health.ebsco.com/products/the-cinahl-database)). There will be no restriction to language of studies. The search strategy will
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33 166 combine validated filters related to ‘systematic reviews and meta-analyses’, ‘physical
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35 167 therapy interventions’ and ‘low back pain’ (See appendix 2 for more details). Two
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37 168 review authors will independently assess and select potential studies to be included
38
39 169 based on titles and abstracts. Any discordance will be resolved by consensus, and if
40
41 170 necessary, a third assessor will arbitrate the final decision. Full-texts of selected
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43 171 systematic reviews will be collected and evaluated in the same manner. After the
44
45 172 process of identification and selection, we will screen the systematic reviews for meta-
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47 173 analyses that fulfill our inclusion criteria. Once we have selected the systematic reviews
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49 174 with the meta-analyses to be included in our study, we will look for the full texts of the
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51 175 RCTs included on these meta-analyses in order to extract their original data. Two
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53 176 authors from our study are trained raters of the PEDro database, so it will be possible to
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3 177 obtain the full texts that are indexed on this database. It is important to state that about
4
5 178 92% of physical therapy RCTs are indexed on the PEDro database.²⁸ For those RCTs
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7 179 not indexed on PEDro, we will make all efforts to get these full texts (searching other
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9 180 databases, contact authors).

181 **Risk of bias assessment (selection and attrition bias)**

182 We will extract the information about selection (allocation concealment) and
183 attrition bias (ITT analysis) from the Physiotherapy Evidence Database (PEDro) for all
184 trials included in the systematic reviews.²⁹ We decided to use the PEDro scale due to
185 the following reasons: 1) the PEDro scale has high reliability for individual ratings and
186 consensus ratings and can be used as a continuous scale for measuring the
187 methodological quality of trials;^{29,30} 2) the PEDro scale is strongly correlated ($r=0.83$;
188 95% CI 0.76 to 0.88) with the Cochrane Risk of Bias tool;³¹ and 3) feasibility: as two
189 authors from this study are raters from the PEDro database, we can easily download the
190 PEDro scores for the included RCTs in our study.

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

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3 202 *all subjects received treatment or control conditions as allocated*".²⁹ Each domain will
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5 203 be rated as 'yes', when the criterion is clearly satisfied, or 'no' when the criterion is not
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7 204 satisfied or the information is unclear in the text. For ITT classification, trials will be
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9 205 rated as 'yes' for ITT analysis, if they use the term 'intention to treat', and it is clear that
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11 206 all subjects received treatment or control conditions as allocated, or that subjects were
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13 207 analyzed according to their initial group allocation. When there are post-randomization
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15 208 exclusions, a trial will be rated as 'no' if the exclusion is on the basis of not receiving
16
17 209 allocated treatment. There are some trials that exclude patients after randomization if
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19 210 authors subsequently realize that the participant was not eligible for the trial.^{32,33} In
20
21 211 this specific case, the trials will be rated as 'yes'. Trials will be rated as 'no', if authors
22
23 212 did not mention any intention to treat approach or reported the use of a modified
24
25 213 intention to treat approach. However, if it is clear that there were no post-randomization
26
27 214 exclusions and all subjects were analyzed according to their initial group allocation, it
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29 215 will be rated as 'yes'.
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34 216 When PEDro score is not available at the PEDro database (the article may not be
35
36 217 indexed in PEDro database; or the article may be in process to be rated), two assessors,
37
38 218 not involved in the study, will independently assess it, using the PEDro rating protocol.
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40 219 Any disagreements will be resolved by discussion or arbitration by a third assessor
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42 220 when consensus cannot be reached. The assessors will be trained raters of the PEDro
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44 221 scale that work in our department and will be blinded to the scope of the manuscript.
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47 222 **Data extraction and synthesis**

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49 223 Two review authors will independently extract data from all trials included in
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51 224 the selected systematic reviews using a standardized extraction form. Any
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53 225 disagreements will also be resolved by discussion or arbitration by a third reviewer
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55 226 when consensus cannot be reached.
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3 227 We will extract bibliographic data (authors, title and year of publication), study
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5 228 characteristics (sample size and interventions used), characteristics of the participants
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7 229 (gender, age, duration and severity of the condition), outcomes results (mean and
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9
10 230 standard deviation). We will only extract outcomes results for the short-term follow-up
11
12 231 (closest to 4 weeks). E-mail requests will be sent to trial authors for additional
13
14 232 information data, when necessary.

16 233 **Data analysis and synthesis**

18 234 In order to determine whether allocation concealment and ITT analysis affect
19
20 235 estimates of treatment effect, a two-level analysis will be conducted. Individual trial
21
22 236 data will be retrieved from the meta-analyses included in our study. Initially, the
23
24 237 treatment effects of each trial will be calculated using mean differences (MD) with 95%
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26 238 confidence intervals for between-group differences at short-term follow-up, or for
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28 239 between-group differences in change scores.^{34,35} Data will be converted to a common 0
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30 240 to 100-point scale if trials had evaluated the same outcome on different scales. Data will
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32 241 be presented separately for each outcome of interest (pain and disability).

34 242 After establishing the treatment effects for the trials included, we will calculate
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36 243 four pooled treatment effect estimates using a random effects model: (i) trials with
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38 244 allocation concealment, (ii) trials without allocation concealment, (iii) trials with ITT
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40 245 analysis and (iv) trials without ITT analysis. This will be done separately for pain and
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42 246 disability outcomes (e.g., a total of eight estimates).

44 247 We will assess between-trial heterogeneity using I-squared test (I^2). This test
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46 248 demonstrates whether the percentage of total variation across studies is explained by
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48 249 heterogeneity rather than chance. An I^2 higher than 75% will be considered as 'high
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50 250 heterogeneity', an I^2 of 50% to 75% will be considered as 'moderate heterogeneity', and
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52 251 an I^2 lower than 25% will be considered as 'low heterogeneity'.³⁶ Review Manager
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3 252 (RevMan) version 5 software will be used for all meta-analyses and heterogeneity
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5 253 assessment.

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7 254 The second stage of the analysis will be a meta-regression to evaluate the
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9 255 association between methodological characteristics of included trials and the estimates
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11 256 of treatment effect.¹¹ The dependent variable will be the treatment effects (mean
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13 257 between-group difference) for the main outcomes (pain or disability), while the
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15 258 independent variables will be the methodological characteristics of interest (allocation
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17 259 concealment and ITT analysis). Additionally, we will add two independent covariates in
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19 260 meta-regression analysis: sample size and sequence generation. We decided to
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21 261 investigate the effect of sequence generation and sample size since these variables have
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23 262 been associated with treatment effect estimates.³⁷ We will extract the information about
24
25 263 sequence generation from the PEDro database and is defined as adequate if “subjects
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27 264 were randomly allocated to groups” (e.g., computer-generated random numbers; coin-
28
29 265 tossing and dice-rolling).²⁹ It will be rated as ‘yes’, when the criterion is clearly
30
31 266 satisfied, or ‘no’ when the criterion is not satisfied or the information is unclear in the
32
33 267 text. The sample size will be considered as a continuous quantitative variable in the
34
35 268 meta-regression model. The covariates will be used according to the number of studies
36
37 269 included (e.g. one covariate for every ten trials). Random-effects meta-regression will
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39 270 be conducted using the ‘metareg’ command in STATA 10 and weighted using effect
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41 271 size standard errors.¹¹

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48 49 273 **DISCUSSION**

50
51 274 To our knowledge, this will be the first study aimed to investigate if the
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53 275 magnitude of the treatment effects of physical therapy interventions in low back pain
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55 276 RCTs is influenced by methodological characteristics (e.g., allocation concealment and
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3 277 ITT analysis). Meta-analyses from RCTs are responsible for the most reliable evidence
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5 278 on the treatment of patients with low-back pain, and their results are of interest to a
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7 279 range of stakeholders.
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9
10 280 However, biased results from RCTs can lead to inadequate clinical decision-
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12 281 making and consequently affect patient outcomes. Clinicians may select interventions
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14 282 for their patients based on trials results that are inflated, and so these are not a very
15
16 283 reliable guide to treatment selection. For example, a systematic review about the
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18 284 effectiveness of low level laser therapy for chronic LBP found a significantly greater
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20 285 reduction in pain in response to laser therapy compared to placebo.³⁸ However, this
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22 286 finding was based on a meta-analysis with three clinical trials that did not conceal
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24 287 allocation or use an ITT analysis, so this result could be an overestimate of the true
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26 288 effect of laser. If this premise of overestimated effect is true, clinicians might in good
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28 289 faith select interventions that are unlikely to help their patients.
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32 290 Therefore, we believe that the findings of this meta-epidemiological study will
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34 291 provide important contributions to clinicians, researchers, and policy-makers in the low-
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36 292 back pain field. This study will improve the available evidence for physical therapists,
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38 293 through the disclosure of reliable and unbiased results on clinical decision-making.
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41 294 The present meta-epidemiological study has several strengths. Since this
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43 295 approach is similar to a systematic review, we will pre-specify methods to identify and
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45 296 select studies to be included through pre-defined inclusion criteria and sensitive search
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47 297 strategy. Data extraction and analysis will be also performed by rigorous methods to
48
49 298 avoid potential bias in this study.
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51
52 299 The limitation of the present study is that it is restricted to meta-analyses of
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54 300 physical therapy interventions in non-specific low back pain. Thus, our results may
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1
2
3 301 have limited generalizability to other interventions as well as to other clinical
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5 302 conditions.

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7 303 **Dissemination**

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9 304 We intend to disseminate our results through presentations at national and
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11 305 international conferences (e.g., World Confederation for Physical Therapy and
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13 306 International Back and Neck Pain Forum) as well as publishing our study in a high-
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15 307 impact international scientific journal.
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21 309 **COMPETING INTEREST**

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23 310 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	<input type="checkbox"/>	1-5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	X	n/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X	<input type="checkbox"/>	54
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	<input type="checkbox"/>	6-14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	<input type="checkbox"/>	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	<input type="checkbox"/>	X	n/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	X	<input type="checkbox"/>	16-19
Sponsor	5b	Provide name for the review funder and/or sponsor	X	<input type="checkbox"/>	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	<input type="checkbox"/>	16-19
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	Appendix 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	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	<input type="checkbox"/>	181-221
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	<input type="checkbox"/>	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	<input type="checkbox"/>	247-251
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X	<input type="checkbox"/>	254-271
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	X	n/a
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective	<input type="checkbox"/>	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)	<input type="checkbox"/>	X	n/a

For peer review only

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.

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3 3 exp LOW BACK PAIN/
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5 4 exp BACKACHE/
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8 5 (lumb\$ adj3 pain).ti,ab,kw.
9
10 6 coccyx.ti,ab,kw.
11
12 7 coccydynia.ti,ab,kw.
13
14
15 8 sciatica.ti,ab,kw.
16
17 9 sciatica/
18
19 10 exp ISCHIALGIA/
20
21 11 spondylosis.mp.
22
23 12 lumbago.ti,ab,kw.
24
25 13 back disorder\$.ti,ab,kw.
26
27 14 or/1-13
28
29 15 systematic review /
30
31 16 meta-analysis /
32
33 17 (#15 OR #16)
34
35 18 (#14 AND #17)
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44 **Cochrane Database of Systematic Reviews**

45
46 #1 MeSH descriptor: [Back Pain] explode all trees
47

48 #2 dorsalgia
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50 #3 backache or back ache
51

52 #4 MeSH descriptor: [Back Pain] explode all trees
53

54 #5 lumb* near pain or coccyx or coccydynia or sciatica or spondylosis
55

56 #6 MeSH descriptor: [Spine] explode all trees
57

58 #7 MeSH descriptor: [Spinal Diseases] explode all trees
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- 3 #8 lumbago or discitis or disc near herniat*
- 4
- 5 #9 spinal fusion
- 6
- 7
- 8 #10 facet near joint*
- 9
- 10 #11 MeSH descriptor: [Intervertebral Disk] explode all trees
- 11
- 12 #12 postlaminectomy
- 13
- 14 #13 arachnoiditis
- 15
- 16
- 17 #14 failed near back
- 18
- 19 #15 MeSH descriptor: [Cauda Equina] explode all trees
- 20
- 21
- 22 #16 lumb* near vertebra*
- 23
- 24 #17 spinal near stenosis
- 25
- 26
- 27 #18 slipped near (disc* or disk*)
- 28
- 29 #19 degenerat* near (disc* or disk*)
- 30
- 31 #20 stenosis near (spine or root or spinal)
- 32
- 33 #21 displace* near (disc* or disk*)
- 34
- 35 #22 prolap* near (disc* or disk*)
- 36
- 37
- 38 #23 MeSH descriptor: [Sciatic Neuropathy] explode all trees
- 39
- 40 #24 sciatic*
- 41
- 42 #25 back disorder*
- 43
- 44 #26 back near pain
- 45
- 46 #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
- 47 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or
- 48 #26)
- 49
- 50 #28 systematic review
- 51
- 52 #29 meta-analysis
- 53
- 54 #30 (#28 or #29)
- 55
- 56 #31 (#27 AND #30)
- 57
- 58
- 59
- 60

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 S7 or 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+")

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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

For peer review only

PRISMA-P 2015 Checklist

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		reporting within studies)			
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For peer review only