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Study Protocol

# Effects of spinal manipulation and pain education on pain in patients with chronic low back pain: a protocol of randomized sham-controlled trial

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ABSTRACT

*Background:* Low back pain (LBP) has more than doubled in the last 20 years, probably influenced by biopsychosocial factors. Noninvasive treatments have been applied in individuals with chronic nonspecific LBP as spinal manipulation and pain education. However, the neurophysiological effects of these treatments are not clear. The aim of this research is to verify the pain control, functional and neurophysiological effects of spinal manipulation, and pain education in individuals with chronic nonspecific LBP.

*Methods:* This research is an assessor and subject blinded, 2-arm, randomized sham-controlled trial and will be conducted at Governador Celso Ramos Hospital, Florianópolis, Brazil. One hundred and twenty-eight individuals with chronic nonspecific LBP will be recruited for this study. Individuals will be randomly allocated into one of the two groups: (1) spinal manipulation plus pain education or (2) sham treatment plus pain education. Each group will be received two sessions per week over six weeks of treatment. The measures will be applied at baseline, six weeks, and three months after randomization. The primary outcome will be a pain intensity at six weeks postrandomization. Secondary outcomes will be pressure pain threshold, disability, fear and avoidance beliefs, kinesiophobia, risk of poor prognosis, quality of life, and inflammatory biomarkers.

*Discussion:* Evidence has shown that psychosocial factors are more involved in chronic pain than we thought a few years ago. Then, studies investigating both functional and neurophysiological effects of these interventions to evaluate the effectiveness of treatment and what else is happening at the cellular level in nervous system are needed.



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## 1. Background

Low back pain (LBP) is the greatest contributor to global disability and the sixth regarding the global burden.[1] Its prevalence has more than doubled in the last 20 years.[2] LBP can be clinically classified into three categories: specific spinal pathology, radicular pain, and nonspecific LBP. Nonspecific LBP is defined as comorbidity without an attributable or recognizable known cause (i.e., tumor, fracture, osteoporosis, and radicular syndrome).[3]

Few studies have suggested possible pathophysiological mechanisms in LBP as the increase of the inflammatory biomarkers tumor necrosis factor-α (TNF-α), interleukins (IL)-1α, IL-1β, IL-6, IL-17, chemokines (CCL) 2 and 4, and a decrease of IL-10, anti-inflammatory cytokines.[4–9] These biomarkers (e.g., cytokines) are small secreted proteins released by immune cells populations, predominantly by T Helper and macrophages cells. They have a specific effect on the interactions and communication between cells.[10]

It is already known that these biomarkers can modulate neuronal activity in various classes of neurons, in both peripheral and central nervous systems. They can modify the individuals' threshold nociception, which may lead to central sensitization and maladaptive brain changes.[11,12] Likewise, not just these biological factors contribute to pain chronification. Other factors such as kinesiophobia, pain catastrophizing, inappropriate beliefs about pain, sleep problems, and depression may also contribute to the central sensitization and pain chronification.[13,14]

Some noninvasive treatments have been used to manage this condition and decrease pain, disability, and psychological factors in individuals with LBP. Diverse types of treatment are used by physical therapists for these individuals such as exercise, manual therapy (e.g., spinal manipulation – SM), and cognitive therapies (e.g., pain education) as part of a biopsychosocial approach.[15–17]

SM alone can reduce pain and disability, change the levels of some blood markers, brain regions, or change the individual's motor control.[18,19] However, changing the individuals' beliefs about movement and pain is also needed.[20] Physical therapists have been using some of the educational interventions to achieve this goal.[21,22] Studies have shown that SM combined with pain education had good results in individuals with LBP.[23,24] Nevertheless, there are no studies that investigated pain control, neurophysiological, and functional effects of manipulative therapy associated with pain education compared to sham treatment plus pain education in individuals with chronic nonspecific LBP.

Therefore, the purpose of this research is to verify the effect of manipulative therapy associated with pain education on the proinflammatory biomarkers and anti-inflammatory cytokines, pain, disability, the risk of poor prognosis and fear and avoidance beliefs, kinesiophobia, quality of life, and pressure pain threshold in individuals with chronic nonspecific LBP.

This study will be a prospective study, assessor and subject blinded, 2-arm, randomized sham-controlled trial with concealed allocation and intention-to-treat approach.

## 2. Methods

### 2.1. Study setting

This research will be conducted in an Orthopedic Physical Therapy Outpatient Service at Governador Celso Ramos Hospital in Florianopolis, Santa Catarina, Brazil. The study start date was in December 2016, and the estimated completion date is in December 2018. This protocol was registered in ClinicalTrials.gov (NCT02982382), World Health Organization (U1111-1190-4899), and approved by the Human Research Ethics Committee of our Institutions (Plataforma Brasil CAAE 52801515.3.0000.0121/CEP-UFSC 1.751.923).

### 2.2. Eligibility criteria

This study will include individuals with chronic episodes of nonspecific LBP for at least six months,[25] 3 points in the Numeric Pain Rating Scale (NPRS), pain during the movement for at least one direction (flexion, extension, side bending, or rotation of the trunk), and aged between 18 and 65 years. They will be excluded if they present the following clinical conditions: (1) previous history of lumbar myelopathy, rheumatic disease, tumors, peripheral, or central neurological disorders; (2) historical of trauma, fracture, or surgery in lumbar region; (3) nerve root compression signs: important muscle weakness affecting lower limb, decrease or abolish of patellar and calcaneus reflex, and decrease of dermatomes sensibility of lower limbs.

### 2.3. Interventions details

After the previous assessment, individuals will be allocated into one of the two groups. In group one, subjects will receive high velocity and low amplitude techniques (HVLA) or grade V manipulation[26] to the lumbar region, and pain education based on the biopsychosocial approach.[15] In group two, individuals will receive sham treatment and pain education.

The technique applied in lumbar region will be the lumbar roll. The symptomatic spinal levels will be selected by physical therapist criteria. In this procedure, the individual will be positioned on the side lying with the supralateral leg in hip and knee flexion with the foot positioned on contralateral popliteal region to manipulate mid lumbar (Fig. 1A), to manipulate lower back, the foot is positioned behind of contralateral ankle (Fig. 1B), and to manipulate upper portion of low back, the foot is positioned behind the thigh in the maximum hip flexion (Fig. 1C), and then the individual's trunk will be rotated contralaterally. The physical therapist will place his forearm in the patient's hip with the fingers located on the individual's supralateral transverse process of lumbar vertebrae; the other forearm will be in the chest/axillar region. The physical therapist forearm located at individual's hip rotates it until the end of the passive range of motion, and then, the physical therapist applies an HVLA movement.[26] The time spent to apply manipulative therapy will be around five minutes.

Pain education will be held for both groups, which consist of a biopsychosocial approach that demystifies behavioral fears and beliefs about pain and movement, explains how

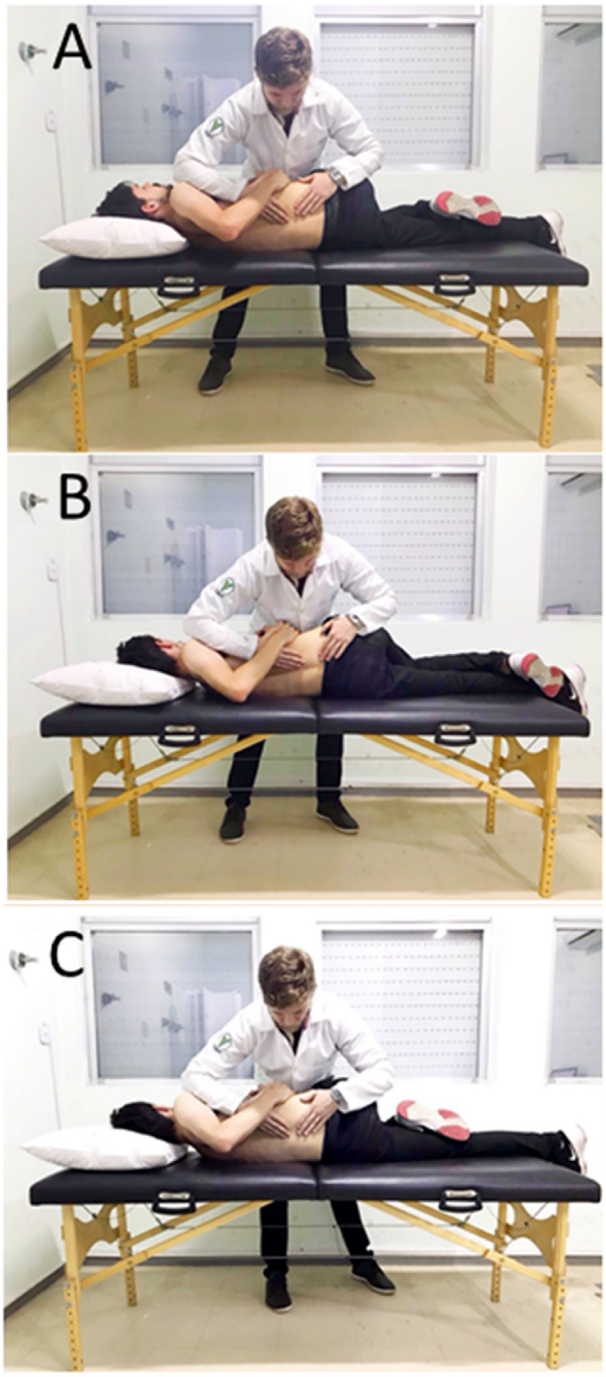


**Fig. 1** – Lumbar roll technique applied in the mid (panel A), lower (panel B), and upper (panel C) portion of individuals' low back.

pain is not always involved with tissue damage or degeneration and how biological, psychosocial, and cognitive factors influence in pain perception.[15,27] In the first session, participants will receive a structured lecture with the main points of this approach as follows: How pain is important to our lives? Pain is a good thing, like an alarm which warns us that something could be wrong. What are the factors that contribute to pain chronification? The importance of psychosocial factors (stress, anxiety, kinesiophobia, etc.) in the pain chronification; the contribution of lack of sleep and physical activity in LBP, gradual exposure in physical activity, and daily movements (i.e., bending down to pick up some object in the ground or tie the shoelace); neurophysiology of pain; and factors such as nocebo effects; no correlation between posture, image exams, and pain.[27–29] In the other sessions will be done the reinforcement of the themes covered in the first session, focusing where individuals have more difficulties to change.

In group two, individuals will receive sham treatment, which consists of manual touch in the lumbar region without any movement for five minutes. The technique must be performed with the individual positioned on the side lying with the supralateral leg in hip and knee flexion (as treatment group), and the individual's trunk will not be rotated contralaterally to avoid vertebrae cavitation. This group will also receive pain education as the treatment group.

The treatment will be performed twice a week during six weeks from both groups and from both groups,[30] with individual sessions held by physical therapists who are experienced in manual therapy and pain education. These therapists trained for six months to standardize the techniques. The treatment will be performed at the Orthopedic Ambulatory of Governador Celso Ramos Hospital.

The therapist who will apply the techniques is a physical therapist with six-year experience in manipulative therapy and three-year experience in biopsychosocial approach; the physical therapist has master's degree in physical therapy and courses related in manual therapy and biopsychosocial approach.

As described in informed consent, individuals will have guarantee rights to leave the study or to change the groups she/he has been allocated at any time of the treatment.

The individuals will be instructed about the importance of the attendance of all treatment sessions. If any individual misses a session, she/he will be contacted by phone to reschedule as soon as possible. The individuals will be advised but not prohibited from taking any concomitant treatments of physical therapy.

### *2.4. Primary and secondary outcome measures and assessment points*

The primary outcome will be a subjective pain after six weeks treatments. Secondary outcomes will be pressure pain threshold, disability, fear and avoidance beliefs, the risk of poor prognosis, kinesiophobia, quality of life, and amount of blood biomarkers. The data related to the research outcomes will be collected by blinded assessors at baseline assessment, after six weeks (all outcomes), and three months after randomization (all outcomes with less blood sample). Details of study design can be found in Fig. 2. The importance of complete follow-up will be made by physical therapists; if any patient discontinues the treatment, they will be contacted by phone to know the reason as to why they cannot continue the treatment; then, the therapist will try convincing them to do the maximum of possible interventions and at least the follow-ups.

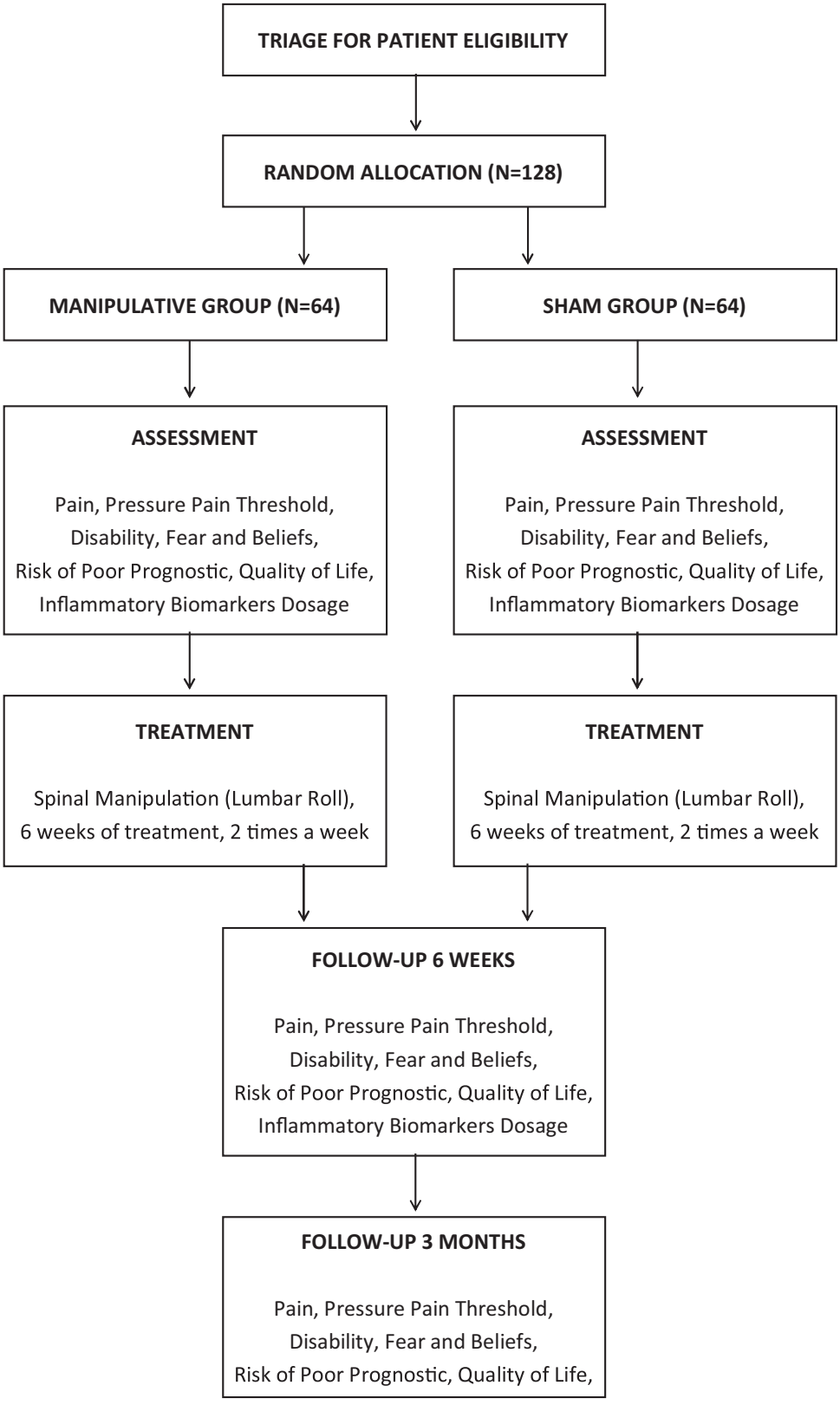


**Fig. 2** – Flow diagram of the study.

#### 2.4.1. *Evaluation of pain*

The Numeric Pain Rate Scale (NPRS) is a unidirectional scale of pain used in adults. It is a numeric version of Visual Analogue Scale, in which an individual chooses a number (minimum of 0 and maximum of 10 points) that better describes the individual's pain intensity (0 represents "no pain," and 10 represents "worst pain ever"). Its intraclass correlation coefficient (ICC) is high (0.96).[31]

#### 2.4.2. *Pressure pain threshold*

The pressure pain threshold will be assessed through an algometer (JTECH Commander, Salt Lake City, EUA). The pressure applied on the individuals' skin will be performed three times in each point (5 cm of both sides of the spinal process of L1, L3, and L5 vertebrae, and on the muscle belly of tibialis anterior muscle). The pressure will be measured in pounds, and the peak pressure will be automatically registered.[32] The mean of three repetitions will be used for statistical analysis. Its ICC to LBP is considered high (0.79).[32,33]

#### 2.4.3. *Disability*

The disability caused by chronic nonspecific LBP will be assessed by Rolland Morris Disability Questionnaire (RMDQ), which has 24 dichotomous yes and no questions. Its score ranges from 0 to 24, whereas as higher is the score, the worst is the disability. Its ICC is considered high (0.80).[34]

#### 2.4.4. *Fear and beliefs about pain*

Fear and beliefs of participants will be assessed using the Fear Avoidance Belief Questionnaire (FABQ). The FABQ has 16 questions; the score of each question varies from 0 to 6 points. This questionnaire is divided into two subscales, with the first part (from 1 to 5) related to physical activity and the second part (from 6 to 16) related to labor activity. Its ICC is high (0.94).[35]

#### 2.4.5. *Risk of poor prognosis*

The STarT Back Screening Tool (SBST)[36] will be used to assess the risk of poor prognosis of individuals with chronic nonspecific LBP. It consists of nine questions, with eight dichotomously score ("agree" or "disagree") and one question related to bothersomeness (which uses a five-point Likert scale). The overall score ranges from 0 to 9. Psychosocial subscale (items 5–9) score ranged from 0 to 5 points. Its ICC is considered as high (0.90).[37]

#### 2.4.6. *Kinesiophobia*

Kinesiophobia will be assessed by Tampa Scale of Kinesiophobia (TSK), and it is an instrument used to assess the individual's fear of executing a movement (ex. Lumbar flexion). It has 17 questions which contemplate themes like pain and symptoms intensity. Scores above 37 points indicate kinesiophobia characteristics and how higher the score, higher the grade of kinesiophobia. Its ICC is considered high (0.95).[38]

#### 2.4.7. *Quality of Life*

The quality of life will be assessed through the Short-Form 12 version 2 (SF-12v2), which is a self-perception evaluation related to health. This assessment includes 12 items that investigate multidimensionally physics and mental health aspects to general people with chronic diseases.[39] Its ICC with SF-36 is high for physical and mental health components (0.97 and 0.98, respectively).[40]

#### 2.4.8. *Blood collection and quantifying the biomarkers amount*

Blood samples will be collected by a trained, licensed nurse; then, it will be processed within 10 minutes of collection by centrifugation at 7000 rpm for 7 minutes at room temperature, and then serum will be stored at −80°C. The amount of proinflammatory and anti-inflammatory biomarkers will be measured through commercial ELISA kits (ImmunoTools GmbH, Germany). The cytokines levels, TNF-α, IL-1β, IL-4, IL-6, IL-8, IL-12/IL23, IL-10, IL-15, MIP-4/CCL18, MCP-3/CCL7, MCP-2/CCL8, IGP – 10/CXCL10, Stromal Lymphopoietin Receptor (TSLR) and Interferon Gamma will be expressed as pg/mL serum. The C-reactive protein (CRP) will be determined through commercial kit (Bioclin, MG, Brazil). These biomarkers will be measured according to manufacturer's instructions in our laboratory by a trained experimenter. The cytokines and CRP measures will be performed in blinded conditions.

### 2.5. *Sample size*

One hundred and twenty-eight individuals, residents of the metropolitan region of Florianopolis, aged from 18 to 65 years with chronic nonspecific LBP for more than 6 months will be recruited.

#### 2.5.1. *Sample size calculations*

The required sample size was calculated assuming a mean difference of 1.5 and a standard deviation of 2.4[41] with a power of 0.9 and a 15% of dropout to six-week follow-up; as a result, the study requires a sample size of 64 per group or 128 individuals in total. The sample size was calculated with software supported by MGH Mallinckrodt General Clinical Research Center (http://hedwig.mgh.harvard.edu/sample_size/js/js_parallel_quant.html). For achieving adequate participant enrollment, participants will be recruited from primary care, community, face-to-face, and by social networking websites.

### 2.6. *Recruitment*

Recruitment of individuals will be conducted from the primary care, community, face-to-face, and by social networking websites.

Individuals' eligibility will be assessed by blinded assessors to determine if they are eligible for this research. Then, they will be informed about the objectives of this study and asked to sign the consent form. Afterwards, the sociodemographic data will be recorded. After baseline assessment, the physical therapist will allocate the individual in one from both groups and will start the correspondent treatment. All data will be stored in Excel (Microsoft Corporation, Redmond, Washington) spreadsheets for future analysis.

### 2.7. *Allocation*

Before the treatment starts, one of the researchers not involved in the recruitment and assessment will allocate the individuals in one of both groups. Each number with

a correspondent group (Manipulation or Sham) will be put inside an opaque sealed envelope, and it will be opened only in the first treatment session. This envelope will be opened, and the treatment group will be seen only by the physical therapist involved in the individuals' treatment.

### 2.8. Blinding

Blinding the therapist will not be possible, given the nature of this research. However, the person who allocates patients, assessors, and patients will be blinded to the treatment groups. Unblinding conditions should occur just in case of medical emergency. Blinding assessment will be applied to assessors and patients, and it will be evaluated by three possible answers (Group 1, 2, or Don't Know).

### 2.9. Data management

After the assessment, all participants receive an identification number and data will be stored in an internet cloud program, hard drive computer, and paper file. All data values will receive a double check by assessors before the analysis.

### 2.10. Statistical analysis

The intention-to-treat principles will be used in this research.[42] The descriptive data and the scores for the primary outcome (NPRS) and secondary outcomes: RMDQ, SBST, FABQ, SF-12v2 and as well as the pressure pain threshold means and the values of inflammatory biomarkers; before, after interventions, and 3 months after randomization will be tabbed on Microsoft Excel 2016. Shapiro–Wilk test will be applied to test the normality distribution of data to compare the groups; depending on this distribution, one-way ANOVA for parametric data or Kruskal–Wallis test for non-parametric data will be used. One-way ANOVA or another Kruskal–Wallis will be applied to compare groups on preintervention, and the data will be presented by mean and standard deviation.

Covariance analysis (ANCOVA) will be conducted to assess the treatment effect on the following outcomes: scores obtained on RMDQ, FABQ, SF-12v2, SBST, and NPRS, pressure pain threshold, and the blood biomarkers concentrations, using the post-treatment means as dependent variables, the pretreatment means as covariables, and the group as a fixed factor.

For these analyses, the Statistical Package for the Social Sciences (IBM SPSS version 20.0, IBM Corp, Armonk, NY) will be used.

### 2.11. Data monitoring, harms, and auditing

The therapists will review all significant adverse events that might occur during the assessment or treatment. The study will be modified or stopped if it is determined by the safety monitor in consultation with the Federal University of Santa Catarina Institutional Review Board (IRB).

Adverse events that are unexpected, related to study procedures, and place individuals at increased risk of harm will be reported to the Santa Catarina Federal University IRB as soon as possible. An adverse event is considered unexpected if it is not a known risk of the study procedures and is not consistent with the expected natural progression of any underlying disease or condition of the participant.

### 2.12. Ethics approval and consent to participate

This study was approved by the Santa Catarina Federal University IRB (#52801515.3.0000.0121). All participants will provide informed consent before participating in this research, which will be collected by the assessor who will allocate the participant. The authors do not have any conflict of interest. If there will be any important modification in the protocol, the relevant parts will be reported, and the amendments will be made to the databases.

The content is uniquely the responsibility of the authors and does not necessarily represent the official views of the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), or Hospital Governador Celso Ramos (HGCR), and they have no ultimate authority over any activity.

Only researchers enrolled in this study will have access to information about individuals. If there is any proven complication that was caused by the treatment, another treatment will be on offer to an individual. If any individual suffers some harm from trial participation, the proper treatment will be offered to help them recover this initial condition.

The final trial data set will be available to the investigators; to ensure confidentially, the data will be blinded to avoid any identifying information.

Once the data have been analyzed and the primary results published, the results of this study will be made publicly available on ClinicalTrials.gov. The full protocol will be available to the public on request.

A person will only be included as an author of this research if she/he makes strong and important contributions to research such as assessing, data analyzing, writing, etc.

## 3. Discussion

### 3.1. Significance of the study

Psychosocial factors are more involved in chronic pain than we thought a few years ago. Up to date, there are no randomized controlled trials investigating and comparing the neurophysiological and functional effects of manipulative therapy associated with pain education in relation to sham treatment in individuals with chronic nonspecific LBP. An appropriate comparison against a sham group will arrange for more unbiased estimates the intervention effects.

Some studies had shown that manipulative therapy and pain education had diminished pain and disability.[20,43,44] However, the majority showed small treatment effect with immediate or short-term effects, mainly in manipulative therapy, and anyone shown the neurophysiological consequence of these interventions in a large symptomatic sample. Understanding the role and the changes of biomarkers after treatment in LBP may suggest the mechanisms involved in

cellular level, and we should rethink about the approaches used to treat this condition.

### 3.2. *Strengths and weakness of the proposed protocol*

This is a prospective registered randomized sham-controlled trial with concealed allocation. An intention-to-treat approach will be used, and the sample size was calculated to provide a statistical power to detect between-groups difference in the outcomes. The assessors and individuals will be blinded to treatment. The Physical Therapists who will apply the treatments both have considerable experience and a Master's Degree in physical therapy. Meanwhile, this trial has some limitations. Unfortunately, the therapist will not be blinded due to the interventions, and one of the themes approached in pain education is a physical activity which depends on participants' enthusiasm. Another limitation is that there are many secondary outcomes that can make type I error.

## Conflict of interest

The authors declare no conflict of interest.

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## References

1. Hoy D, March L, Brooks P, Blyth F, Woolf A, Bain C, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014;73:968–74, http://dx.doi.org/10.1136/annrheumdis-2013-204428.
2. Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, et al. The rising prevalence of chronic low back pain. *Arch Intern Med* 2009;169:251, http://dx.doi.org/10.1001/archinternmed.2008.543.
3. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006;15(S2):s192–300, http://dx.doi.org/10.1007/s00586-006-1072-1.
4. Igarashi A, Kikuchi S, Konno S, Olmarker K. Inflammatory cytokines released from the facet joint tissue in degenerative lumbar spinal disorders. *Spine (Phila Pa 1976)* 2004;29:2091–5, http://dx.doi.org/10.1097/01.brs.0000141265.55411.30.
5. Risbud MV, Shapiro IM. Role of cytokines in intervertebral disc degeneration: pain and disc content. *Nat Rev Rheumatol* 2013;10:44–56, http://dx.doi.org/10.1038/nrrheum.2013.160.
6. Solovieva S, Leino-Arjas P, Saarela J, Luoma K, Raininko R, Riihimaki H. Possible association of interleukin 1 gene locus polymorphisms with low back pain. *Pain* 2004;109:8–19, http://dx.doi.org/10.1016/j.pain.2003.10.020.
7. Li Y, Liu J, Liu Z-z, Duan D-p. Inflammation in low back pain may be detected from the peripheral blood: suggestions for biomarker. *Biosci Rep* 2016, http://dx.doi.org/10.1042/BSR20160187.
8. Wang H, Glauben R, Gebhard K, Buchner M, Schiltenwolf M, Raum E, et al. High serum level of Tnf-A correlates with chronic low back pain but not acute sciatica. *Eur Cells Mater* 2005;10:33.
9. Teodorczyk-Injeyan JA, McGregor M, Triano JJ, Injeyan HS. Elevated production of nociceptive CC-chemokines and sE-selectin in patients with low back pain and the effects of spinal manipulation: a non-randomized clinical trial. *Clin J Pain* 2017;1, http://dx.doi.org/10.1097/AJP.0000000000000507.
10. Zhang J-M, An J. Cytokines, inflammation, and pain. *Int Anesthesiol Clin* 2007;45:27–37, http://dx.doi.org/10.1097/AIA.0b013e318034194e.
11. Dinarello CA. Proinflammatory cytokines. *Chest* 2000;118:503–8, http://dx.doi.org/10.1378/chest.118.2.503.
12. Hotz-Boendermaker S, Marcar VL, Meier ML, Boendermaker B, Humphreys BK. Reorganization in secondary somatosensory cortex in chronic low back pain patients. *Spine (Phila Pa 1976)* 2016;41:E667–73, http://dx.doi.org/10.1097/BRS.0000000000001348.
13. Uluğ N, Yakut Y, Alemdaroğlu İ, Yılmaz Ö. Comparison of pain, kinesiophobia and quality of life in patients with low back and neck pain. *J Phys Ther Sci* 2016;28:665–70, http://dx.doi.org/10.1589/jpts.28.665.
14. Pakpour AH, Yaghoubidoust M, Campbell P. Persistent and developing sleep problems: a prospective cohort study on the relationship to poor outcome in patients attending a pain clinic with chronic low back pain. *Pain Pract* 2017, http://dx.doi.org/10.1111/papr.12584.
15. Meziat Filho N, Mendonça R, Nogueira LAC. Lack of confidence in the lower limb: Cognitive Functional Therapy (CFT) for a unilateral loading impairment in chronic non-specific low back pain. Case report. *Man Ther* 2016, http://dx.doi.org/10.1016/j.math.2016.02.007.
16. Chou R, Deyo R, Friedly J, Skelly A, Hashimoto R, Weimer M, et al. Nonpharmacologic therapies for low back pain: a systematic review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017;166:493–505, http://dx.doi.org/10.7326/M16-2459.
17. Paige NM, Miake-Lye IM, Booth MS, Beroes JM, Mardian AS, Dougherty P, et al. Association of spinal manipulative therapy with clinical benefit and harm for acute low back pain. *JAMA* 2017;317:1451, http://dx.doi.org/10.1001/jama.2017.3086.
18. Kolberg C, Horst A, Moraes MS, Duarte FC, Riffel AP, Scheid T, et al. Peripheral oxidative stress blood markers in patients with chronic back or neck pain treated with high-velocity, low-amplitude manipulation. *J Manipulative Physiol Ther* 2015;38, http://dx.doi.org/10.1016/j.jmpt.2014.11.003.
19. Haavik H, Murphy B. The role of spinal manipulation in addressing disordered sensorimotor integration and altered motor control. *J Electromyogr Kinesiol* 2012;22:768–76, http://dx.doi.org/10.1016/j.jelekin.2012.02.012.
20. Meziat Filho N. Changing beliefs for changing movement and pain: classification-based cognitive functional therapy (CB–CFT) for chronic non-specific low back pain. *Man Ther* 2016;21:303–6, http://dx.doi.org/10.1016/j.math.2015.04.013.
21. Louw A, Louie PE, Mintken P. Use of an abbreviated neuroscience education approach in the treatment of chronic low back pain: a case report. *Physiother Theory Pract* 2012;28:50–62, http://dx.doi.org/10.3109/09593985.2011.562602.

22. Moseley GL, Nicholas MK, Hodges PW. A randomized controlled trial of intensive neurophysiology education in chronic low back pain. *Clin J Pain* 2004;20:324–30 http://www.ncbi.nlm.nih.gov/pubmed/15322439.
23. Puentedura EJ, Flynn T. Combining manual therapy with pain neuroscience education in the treatment of chronic low back pain: a narrative review of the literature. *Physiother Theory Pract* 2016:1–7, http://dx.doi.org/10.1080/09593985.2016.1194663.
24. Brismée J-M, Sizer PS. Orthopaedic manual physical therapists – champions in education, manipulative therapy and movement control restoration. *J Man Manip Ther* 2015;23:171–2, http://dx.doi.org/10.1179/1066981715Z.000000000150.
25. *Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms*. 2nd ed. Seattle: IASP Press; 1994.
26. Maitland G, Hengeveld E, Banks K, English K. *Maitland's vertebral manipulation*. 7th ed. Edinburgh: Elsevier; 2005.
27. Nijs J, Meeus M, Cagnie B, Roussel NA, Dolphens M, Van Oosterwijck J, et al. A modern neuroscience approach to chronic spinal pain: combining pain neuroscience education with cognition-targeted motor control training. *Phys Ther* 2014;94:730–8, http://dx.doi.org/10.2522/ptj.20130258.
28. Nijs J, Paul van Wilgen C, Van Oosterwijck J, van Ittersum M, Meeus M. How to explain central sensitization to patients with "unexplained" chronic musculoskeletal pain: practice guidelines. *Man Ther* 2011;16:413–8, http://dx.doi.org/10.1016/j.math.2011.04.005.
29. Vlaeyen JWS, Crombez G, Linton SJ. The fear-avoidance model of pain. *Pain* 2016;157:1588–9, http://dx.doi.org/10.1097/j.pain.0000000000000574.
30. Haas M, Vavrek D, Peterson D, Polissar N, Neradilek MB. Dose-response and efficacy of spinal manipulation for care of chronic low back pain: a randomized controlled trial. *Spine J* 2014;14:1106–16, http://dx.doi.org/10.1016/j.spinee.2013.07.468.
31. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)* 2011;63(S11):S240–52, http://dx.doi.org/10.1002/acr.20543.
32. Farasyn A. *Pressure pain algometry in patients with non-specific low back pain*; 2007 http://www.roptrotherapy.info/nl/doc/phd-farasyn.pdf.
33. Fischer AA. Pressure algometry over normal muscles. Standard values, validity and reproducibility of pressure threshold. *Pain* 1987;30:115–26 http://www.ncbi.nlm.nih.gov/pubmed/3614975.
34. Nusbaum L, Natour J, Ferraz MB, Goldenberg J. Translation, adaptation and validation of the Roland-Morris questionnaire – Brazil Roland-Morris. *Brazilian J Med Biol Res* 2001;34, http://dx.doi.org/10.1590/S0100-879X2001000200007.
35. Waddell G, Newton M, Henderson I, Somerville D, Main CJ. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. *Pain* 1993;52:157–68 http://www.ncbi.nlm.nih.gov/pubmed/8455963.
36. Pilz B, Vasconcelos RA, Marcondes FB, Lodovichi SS, Mello W, Grossi DB. The Brazilian version of STarT Back Screening Tool – translation, cross-cultural adaptation and reliability. *Brazilian J Phys Ther* 2014;18:453–61, http://dx.doi.org/10.1590/bjpt-rbf.2014.0028.
37. Bruyère O, Demoulin M, Beaudart C, Hill JC, Maquet D, Genevay S, et al. Validity and reliability of the French version of the STarT back screening tool for patients with low back pain. *Spine (Phila Pa 1976)* 2014;39:E123–8, http://dx.doi.org/10.1097/BRS.0000000000000062.
38. Siqueira FB, Teixeira-Salmela LF, Magalhães Lde C. Análise das propriedades psicométricas da versão brasileira da escala tampa de cinesiofobia. *Acta Ortopéd Bras* 2007;15:19–24, http://dx.doi.org/10.1590/S1413-78522007000100004.
39. Damásio BF, Andrade TF, Koller SH. Psychometric properties of the Brazilian 12-Item Short-Form Health Survey Version 2 (SF-12v2). *Paid (Ribeirão Preto)* 2015;25:29–37, http://dx.doi.org/10.1590/1982-43272560201505.
40. Iraurgi Castillo I. A comparative analysis of SF-12 with the SF-36 among patients in methadone treatment. *Adicciones* 2007;19:59–67 http://www.ncbi.nlm.nih.gov/pubmed/17687883.
41. Childs JD, Piva SR, Fritz JM. Responsiveness of the numeric pain rating scale in patients with low back pain. *Spine (Phila Pa 1976)* 2005;30:1331–4, http://dx.doi.org/10.1097/01.brs.0000164099.92112.29.
42. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;319:670–4 http://www.ncbi.nlm.nih.gov/pubmed/10480822.
43. de Oliveira MM, Andrade SSCA, de Souza CAV, Ponte JN, Szwarcwald CL, Malta DC. Problema crônico de coluna e diagnóstico de distúrbios osteomusculares relacionados ao trabalho (DORT) autorreferidos no Brasil: Pesquisa Nacional de Saúde, 2013. *Epidemiol Serv Saúde* 2015;24:287–96, http://dx.doi.org/10.5123/S1679-49742015000200011.
44. Hidalgo B, Detrembleur C, Hall T, Mahaudens P, Nielens H. The efficacy of manual therapy and exercise for different stages of non-specific low back pain: an update of systematic reviews. *J Man Manip Ther* 2014;22:59–74, http://dx.doi.org/10.1179/2042618613Y.0000000041.