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Efficacy of Chiropractic Spinal Manipulative Therapy in Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial

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Abstract

Introduction

Chronic low back pain (CLBP) is a highly prevalent and disabling condition. Identifying subgroups of patients afflicted with CLBP is an urgent research priority. A classification system based on pain mechanisms involved in CLBP has been proposed. Spinal manipulative therapy (SMT) is recommended for the management of CLBP. Yet, little data are available regarding its mechanisms of action, making it difficult to match this intervention to the patients who may benefit the most. It was suggested that SMT may influence mechanisms associated to central sensitisation. Therefore, classifying CLBP patients' according to the mechanisms involved may help predict their response to SMT.

Methods and analysis

This protocol describes a randomised placebo-controlled trial aiming to identify variables linked to central sensitisation that may help predict the response to SMT in patients with CLBP. One hundred patients with chronic primary low back pain will be randomized to receive twelve sessions of SMT or placebo SMT over a 4-week period. Pain intensity and disability (measured by the Oswestry Disability Index) will be assessed as primary outcomes upon completion of treatment, and at 4- and 12-week follow-ups. Mixed analyses of variance will be conducted to compare the primary outcomes between groups (SMT vs. placebo) over time (baseline vs. post-treatment). Baseline values of the pain catastrophizing scale and central sensitisation inventory scores, pressure pain thresholds, urinary concentrations of TNF-α and expectations of pain relief will be entered as predictors of the response to SMT in a multiple regression model. Changes before and after treatment in these outcomes will be introduced in a second model to answer the

mechanistic question. Simultaneously, reference values of these predictors will be measured from fifty age and sex-matched healthy controls.

Ethics and dissemination: Ethical approval was granted by the Fundación Jiménez Díaz Clinical Research Ethics Committee.

Trial registration number: NCT05162924

Keywords: Randomized controlled trial; Low back pain; Patient stratification; Central Sensitization; Chiropractic Manipulation

Strengths and limitations of this study:

- This study will expand our understanding on the relevance of clinical, psychological, psychophysical and inflammatory variables in predicting the response of patients with chronic low back pain to manual therapy.
- The design will allow to confirm the usefulness of a classification system for patients with chronic low back pain according to the pain mechanisms involved.
- The blinding of participants (and its assessment), outcome assessors, statistician, laboratory technician, and of the clinician delivering care to the patients' progress will substantially contribute to bias reduction.
- Manual therapy trials are inherently limited by difficulties in blinding participants and the impossibility of blinding the clinician providing care to the intervention.

Introduction

Low back pain (LBP) is the single most important cause of disability globally,[1] with a high proportion of patients whose pain persists or recurs.[1-4] Aiming to identify patient profiles that respond more favourably to specific treatments and their prognosis, recent investigations highlight the importance of identifying subgroups among people with chronic LBP (CLBP). One of the better studied classification systems stratifies patients in specific subgroups according to pain mechanisms (nociceptive, neuropathic or nociplastic).[5-10] It has been suggested that a large share of CLBP patients presents chronic primary pain, which has been linked to altered nociceptive processing.[11 12] Among the phenomena that may underlie this aberrant nociception (nociplastic pain), central sensitization (CS) is likely the predominant mechanism,[12] and its involvement in CLBP deserves further research.[13]

One of the currently recommended interventions for the management of CLBP is spinal manipulation therapy (SMT).[14 15] However, this does not imply that all patients have an identical response.[16] There is insufficient data to determine which CLBP subgroups respond better to this intervention.[17 18] This may be so because the pain-relieving mechanisms are still largely unknown. It was proposed that SMT acts via mechanisms of segmental pain inhibition[19] that influence temporal summation of pain.[20 21] Temporal summation and its maintenance can be useful to identify a CS phenotype.[22-24] Further, emerging data from animal and human studies support the hypothesis that SMT modulates the inflammatory response, influencing inflammatory cytokines.[25-28] Inflammatory cytokines can induce neuroinflammation, which may mediate the development of CS[29 30] in the transition towards chronic pain.[8 31] SMT may thus relieve CLBP by impacting mechanisms linked to CS.[32-35]

Altered pain sensitivity in a specific musculoskeletal region may indicate nociplastic pain, possibly reflecting CS.[12] Abundant studies have reported that a subgroup of CLBP patients demonstrate segmental mechanical hyperalgesia, assessed via lower pressure pain thresholds (PPTs) in lumbar or lower extremity areas when compared to healthy controls.[36-41] Changes in pain sensitivity are not confined to lumbar segments but rather may be present in remote anatomical locations.[13 37 42-44] An increased pain sensitivity is a clinical indicator possibly reflecting CS not just at the spinal level, but potentially implicating supraspinal structures.[8 13 31] Thus, it is plausible that CS may play an important role in defining a CLBP phenotype.[45]

Pain catastrophising has been described as a psychological trait and pain cognition linked to the development of CLBP with an altered pain sensitivity profile and a CS phenotype.[46-48] CLBP patients with higher pain sensitivity often demonstrate higher levels of catastrophising and other negative psychological traits[32 49-51] Similarly, higher pain catastrophising was associated with higher central sensitization inventory (CSI) scores.[52] The CSI and a clinical presentation suggestive of CS mechanisms has been proposed to identify a specific CLBP subgroup.[5 6 53 54]

Currently, the mechanisms leading to CS are still unknown, however, recent data suggest an important role for neuroinflammation.[29] Neuroinflammation may act at multiple levels, from the periphery[50] to the brain,[55] including the dorsal horn of the spinal cord.[56] The release of inflammatory cytokines, including the pro-inflammatory tumour necrosis factor alpha (TNF-α), was identified as a potential mechanism supporting this phenomenon.[29 30 57] Studies have shown an association between proinflammatory cytokines and CLBP,[58-61] suggesting that these may serve as a reliable biomarker to identify patients with a CS phenotype.

Recent data suggest that CS may influence changes in pain sensitivity induced by SMT,[32], however, pain phenotyping has been scarcely applied to manual therapy research.[62] Therefore, it has not yet been possible to assess the response of this subgroup of patients to SMT. The aim of this clinical trial is to investigate whether variables associated with a CS phenotype may help to predict the response to SMT. The specific aims are to identify the clinical, psychological, psychophysical and inflammatory variables linked to CS present in a cohort of CLBP patients; and to examine which of these variables help predict or are associated with the clinical response to SMT.

Methods

Experimental design and setting

The study consists of a mechanistic randomized placebo-controlled clinical trial with a mixed experimental design, whose objective is to assess which variables linked to CS in chronic pain patients can predict the response of CLBP patients to SMT (Figure 1). This protocol followed the guidelines for clinical trial protocols Standard Protocol Items: Recommendations for Interventional Trials[63] (SPIRIT statement). Starting in November 2021, 150 participants will be recruited through the Madrid College of Chiropractic (MCC) teaching clinic in San Lorenzo de El Escorial (Spain). This includes 100 patients with CLBP and 50 healthy participants. Clinical, psychological, psychophysical and inflammatory variables will be measured in CLBP patients, which will be exposed to either SMT or a placebo SMT for 12 visits over a 4-week period. A group made up of 50 age and sex-matched healthy volunteers will be used to determine the reference values of the psychological, psychophysical and inflammatory variables in a healthy population and compare them with the clinical population, before and after exposure.

Selection criteria

To be eligible to participate in the study, patients must be 18 to 70 years old, receive a diagnosis of chronic primary LBP of at least 3-month duration, with or without leg pain (according to a clinical examination carried out at the MCC). If pain affecting the low back or lower limb is suspected to be predominantly of neuropathic origin, the patient will be excluded.[12] Additionally, patients will be excluded from the study if they present any of the following criteria: evidence of specific pathology as the cause of their CLBP, diagnosis of mental illness (with the exception of anxiety and depression, as these conditions are frequently comorbid with CLBP[64 65] and may suggest a CS phenotype[5 49]), presence of pain of equal or higher intensity affecting any other body region, use of corticosteroids, opiates or anti-cytokine medication, pregnancy, lumbar fusion surgery or recent laminectomy, having received chiropractic SMT in the 12 months prior to the beginning of the study.[5 50 51]

A cohort of healthy volunteers will be recruited to be used as a reference for the psychological, psychophysical and inflammatory variables collected in the sample of CLBP patients. They will be age and sex-matched to the patients allocated to the group receiving SMT. Individuals meeting the following criteria are eligible to participate: being 18 to 70 years old; presenting no current or chronic pain condition, as well as not having received any diagnosis of a systemic, inflammatory, neurological or psychiatric condition.

Randomisation, concealed allocation, and blinding

A computer application (random-number generator) will be used to generate a balanced randomisation sequence. Participants will be allocated in a 1:1 ratio to the

intervention (SMT) or placebo arms following the chronological order of recruitment. Patients, outcome assessors and statistician will be blinded to group allocation. To confirm the efficacy of the patients' blinding, participants will respond in three occasions to the questions: "Do you think that the treatment you have received is a real chiropractic treatment for back pain?"; and "On a numerical rating scale of 0–100, please rate the degree of certainty for having received a real chiropractic treatment" (with 0 being total uncertainty and 100 being absolute certainty).[66]

Additionally, to avoid biases in the reporting of patient-reported outcome measures and to blind the investigator delivering the interventions, participants will provide these data via electronic questionnaires without the presence or interference of any investigator.

Interventions

Both real and placebo SMT will be delivered by a chiropractor with 20 years of experience. Real SMT will be performed with the patient positioned in the lateral decubitus position, and applying a high-speed, low-amplitude force on each side of the manipulated segment, with the aim of generating at least one joint cavitation (perceptible sound). For this, the chiropractor will use the hypothenar surface or the last phalanx of the 2nd and / or 3rd fingers of the hand to contact the spinous process of the vertebral segment with the most intense clinical pain, as detected in the initial patient examination. In case of not perceiving a cavitation or satisfactory joint movement, the SMT will be repeated once at the corresponding side. The placebo arm will receive a validated sham SMT, with the patient in the same lateral decubitus position, with the lower leg extended and the upper leg flexed, and an unintended force is applied bilaterally to the gluteal region.[66] Participants in both groups will receive 3 treatment session per week for 4

weeks (see Figure 2–3). Healthy volunteers will receive no intervention during the same time frame of 4 weeks.

Outcome variables

Primary outcomes

Patients will evaluate the intensity of their CLBP at the current time, as well as the mean, minimum and maximum pain throughout the preceding seven days or since the time of the previous session, once the study is underway,[67 68] using a numerical rating scale between 0 (no pain) and 100 (maximum pain imaginable). The baseline and final values of mean pain intensity will be used for statistical analyses. The other primary outcome will be the degree of disability provoked by CLBP. Upon completing the case history, patients will fill out the Oswestry low back disability index questionnaire,[69] which will also be completed at the end of the study. Primary outcomes will also be assessed 4 and 12 weeks after completion of the study for follow-up.

Secondary outcomes

Five topics were identified to discriminate pain mechanisms between groups of patients, including CS mechanisms: clinical examination, questionnaires, quantitative sensory testing, laboratory tests, and imaging tests [9]. In the present study, all categories will be considered except the last one, which will only be taken into account to rule out pain of suspected neuropathic aetiology.

Clinical examination variables

Data on the characteristics of the patients' CLBP will be collected at baseline for exploratory purposes: CLBP trajectory (duration and frequency) and localization. For the later, patients will also draw the area affected by their pain on a tablet, using an

application (Symptom Mapper) that will allow to calculate the degree of pain widespreadness.[70] Additionally, clinicians will determine whether the CLBP is proportionate or disproportionate to the degree or nature of the injury or pathology, with a discrete or diffuse distribution, according to criteria that were defined in the literature.[5 6] A diffuse rather than a discrete distribution was identified as a key criterion suggesting a CS phenotype.[5 12]

Finally, other variables will be reported such as the intake of pain medication compatible with the selection criteria, both at baseline and at after treatment. Similarly, whether the patient regularly smokes will be documented, since smoking has been associated with increased serum levels of pro-inflammatory cytokines.[71] The average number of hours of sleep will also be recorded, as it may help predict pain patterns.[72] Additionally, the presence of any chronic condition (including pain) that are comorbid with the CLBP will be recorded for exploratory purposes.

Questionnaire variables

The Pain Catastrophizing Scale (PCS) and CSI will be completed before the beginning and upon completion of the study.[73 74] The PCS will be used to identify specific pain cognitions that are usually present in patients with a CS phenotype, this measure will be used to evaluate the association of CLBP with psychosocial factors described by Smart et al.[5] The CSI is an excellent tool to identify patients compatible with CS mechanisms, particularly when using the cut-off value of 40 points.[75] Both these scores will be examined as predictors due to their intrinsic association with a CS phenotype.

In addition, the Beck Depression Inventory II (BDI-II) and the Generalized Anxiety Disorder scale (GAD) questionnaires will be used to screen and quantify symptoms of depression and anxiety.[76 77] The scores in these questionnaires will be measured both at baseline and follow-up for exploratory purposes and to determine

whether significant correlations exist between any of these variables and the primary outcomes of pain and disability. Pre and post reference values of all questionnaires (PCS, CSI, BDI-II and GAD) will be taken from the healthy population sample in the same timeframe.

Quantitative sensory testing variables

Quantitative sensory testing based on the German protocol[78 79] will be performed with the aim of evaluating pain thresholds and sensitivity (see Figure 2–2). Testing will consist of the exploration of the PPTs in deep tissues (Figure 3), using an algometer (Wagner Force Dial FPX, Greenwich, CT, USA). In addition, patients will assess the intensity of the first stimulus above threshold, using a numerical rating scale 0–100.[80] Two measurements will be taken bilaterally at a rate of about 50 kPa/s, and the arithmetic mean of both the thresholds and sensitivities reported calculated. Two repetitions of the measurements provide excellent reliability in a population with LBP,[81] while performing two repetitions per side of the lower back was proposed to optimize inter-session reliability.[82] PPTs will be performed over muscle tissue in 4 different locations. Primary pain will be assessed 2.5 cm lateral to the spinous process in the erector spinae[80] of the vertebral segment with the highest clinical pain intensity indicated by the patient and verified by palpation (Figure 3). This will allow the local segmental sensitivity to be assessed. In addition, PPTs will be measured on both lower limbs in the dermatome corresponding to the segment of highest clinical pain intensity (dermatomal sensitivity), in the erector spinae four to six segments cranial to the most painful lumbar segment (heterosegmental sensitivity in a non-symptomatic segment: secondary hyperalgesia), and in a control zone in both thenar eminences (widespread sensitivity). PPTs will be assessed during the initial examination and after the final treatment session (see Figure 2). Reference values will be taken in healthy volunteers in the same locations as the CLBP

participants receiving SMT (lumbar segmental, dermatomal, heterosegmental, widespread), in the same timeframe.

Laboratory test variables: TNF-α as an inflammatory biomarker in urine

Before initiating the first treatment session and on the day of the last one, urine samples will be collected from all patients (first morning micturition), which will be immediately stored at -20ºC (see Figure 2–1). Additionally, the first morning micturition will be collected twice from healthy individuals in the same timeframe (two samples with a 4-week delay).[61] Samples will be deidentified by using only the participant's ID code, and the laboratory technicians will be blinded to group allocation. TNF-α values, including urinary concentrations, were found to be elevated in CLBP patients and may respond to a treatment based on SMT.[25 27 58 61 83] Therefore, urine concentrations of TNF-α will be quantified for each sample using specific ELISA for TNF-α following manufacturer's instructions. The cytokine to creatinine ratio will be calculated to correct for differences in urine volumes.[84]

Expectations

Before initiating treatment, each participant will be asked about their expectations of pain relief upon completion of the study. To do this, a verbal evaluation will be provided using a visual analogue scale with the descriptors -100, equivalent to "total pain relief," 0, equivalent to "no change," up to +100, equivalent to "maximum pain increase". Such an assessment of patients' expectations allows to identify their contribution as part of the placebo response, which were found to predict the response to treatment for chronic pain.[85]

Adverse events reporting

At the beginning of every SMT or placebo treatment sessions, patients will inform whether they have suffered any adverse effects that they feel could be related to the

treatment received via an electronic questionnaire. Adverse effects will be classified into four categories most frequently reported after lumbar SMT as identified in a clinical trial: muscle stiffness, increased pain, radiating discomfort, and others.[86] In addition, patients will indicate whether they were triggered immediately, up to 24 hours, or more than 24 hours after the previous session, whether their duration was of minutes, hours (< 24 hours), between 24 and 48 hours, or longer than 48 hours,[86] and according to their intensity (very mild, mild, moderate, severe, very severe). The reporting of adverse events will be monitored by an investigator not involved in clinical care or examination. A 30-point increase in pain intensity or the reporting of moderate to severe adverse events in three consecutive visits will raise the alert and the patient will be interviewed to determine whether care should be interrupted.

Procedures

Candidates interested in participating in the study will initially complete a form with the selection criteria (Supplemental Appendix 1). If the criteria are met, patients will schedule an appointment at the MCC clinic where they will read and sign a participant information sheet, and the informed consent (Supplemental Appendices 2 and 3). Subsequently, patients will undergo a clinical examination (consisting of a case history and physical examination) to confirm the diagnosis of chronic primary LBP, during which all outcomes will be collected, except for the urine sample that will be provided before the first treatment session. Patients will then participate in 12 treatment sessions divided into 3 weekly sessions for 4 weeks. Meanwhile, healthy volunteers will participate in two visits (baseline and follow-up after 4 weeks) when all relevant outcomes will be assessed (Figure 2). Once this phase of the study has been completed, all patients will be contacted to request that they provide data on CLBP intensity and disability 4 and 12 weeks after

completing the study (Figure 1). Patients allocated to the placebo arm will be offered the possibility of receiving the equivalent "real" SMT at the MCC free of charge. The study will have a total estimated duration of one year.

Sample size calculation

To determine the ideal number of participants, the first aim to identify the variables linked to a CS phenotype that could help predict the response to treatment based on SMT for CLBP was considered. A multiple regression analysis will be performed, using five independent variables described in the statistical analysis section as predictors. The baseline values of these variables will be included in the multiple regression model. For each predictor variable, it is recommended to estimate about ten sample elements, therefore we predict that a sample size of 50 patients per group will be necessary.[87]

Regarding the two primary outcome variables (pain intensity and disability related to CLBP), a reduction in pain and disability after one month in patients who receive 12 sessions of SMT compared to placebo will be expected. We aim to detect small to moderate effects since it is a one-month intervention in patients with chronic pain unresolved by other treatments over at least 3 months. Therefore, based on an effect size of f = 0.175, an alpha of 0.05, a power of 0.8 for 2 groups and 2 repeated measures (baseline and session 12), and a correlation between the repeated measures of 0.5, the size of the necessary sample is 34 patients per group, thus a total of 68 patients to detect statistically significant changes in clinical pain and disability. Therefore, the analysis based on the regression model to predict the clinical course provides with a large enough size for both the first and second aims of this study.

Statistical analysis

As recommended by White et al., efforts will be directed towards following up all participants for every time point.[88] An intention-to-treat analysis including all randomized study participants with a baseline endpoint assessment will be performed. The use of mixed model ANOVA allows to include all study participants with a lower attrition bias,[89] while handling missing data using maximum likelihood estimations. Further, a per-protocol analysis will be also performed excluding study participants who voluntarily drop out from the study, develop a severe adverse reaction (increase in >30 points average pain intensity associated to treatment) or fail to attend three consecutive visits, or more than two treatment weeks. Finally, in order to test whether the data is not missing at random, a sensitivity analysis will be conducted to explore the effect of attrition [88].

The normal distribution of the data will be verified using the Kolmogorov-Smirnov test. Data deviating from normality will be transformed to obtain a normal distribution before being entered into the data analysis. The two main outcome variables (clinical pain intensity and disability) will be compared between groups (SMT vs. placebo) over time (baseline and post-treatment) using a mixed analysis of variance. Average pain intensity since the last treatment visit and in the seven days prior to the initial visit will be the variable used for statistical analyses. With an exploratory objective, the secondary variables (PCS, CSI, BDI-II, GAD scores, PPTs, degree of pain widespreadness, urinary cytokine levels, number and severity of reported adverse effects, presence of leg pain, pain medication use) will be compared between groups (SMT vs placebo) over time (baseline and post-treatment) using another mixed analysis of variance. To test a priori hypotheses, significant effects will be decomposed using planned comparisons. For the rest of the effects, Tukey's HSD will be used for testing any pair-wise comparisons between group means.

Pearson's product-moment correlation analyses will be carried out to examine the association between primary variables and secondary variables that demonstrate significant effects between groups over time. Subsequently, two multiple regression models will be used to examine the predictors of improvement in clinical pain and disability over time in patients who have received SMT. The secondary variables used for this analysis will be: baseline PCS and CSI score, baseline PPTs in the primary pain region, baseline TNF-α levels, and baseline expectations of pain relief. In addition, in another regression model, the changes (delta) in these variables (except expectations of pain relief, since they are only measured a priori) after 4 weeks of treatment will be used as predictor variables. This is done to identify the variables most associated with clinical evolution to answer the mechanistic question.

In order to interpret the values in outcomes measured in patient groups, these will be compared with reference values obtained from the healthy controls to the CLBP group receiving SMT. This will allow characterizing the patients' groups to determine whether they show increased psychological symptoms, pain sensitivity and hyperalgesia as well as increased TNF-α levels compared with a reference healthy population. A series of mixed analyses of variance will be performed to examine differences in PPTs, urinary TNF-α levels, PCS, CSI, BDI-II and GAD scores before and after treatment between the three groups (control, SMT and placebo). To test a priori hypotheses, significant effects will be decomposed using planned comparisons. For the rest of the effects, Tukey's HSD will be used for testing any pairwise comparisons between group means.

Data management and monitoring

All data will be collected at the MCC teaching clinic of the Real Centro Universitario María Cristina. The clinic utilizes a password-protected computer app that

generates a patient file number linked to their clinical and personal data. This file number will be connected to a unique participant ID code made up of three numbers and a letter. This ID code will be used to deidentify all clinical trial data. Only the investigator involved in delivering care will have knowledge of which clinic file number corresponds to which study ID code. The participants' selection, information, consent forms and outcome measures collected in paper format will be securely stored in a file cabinet at the MCC clinic. Patient-reported outcome measures will be collected electronically using the study ID code to complete a google form (Google Inc.). Both paper and online data will be transferred to a password-protected spreadsheet, only accessible to the principal investigator. Data will be stored deidentified for 25 years after final publication. The dataset will be made available after publication of the trial, upon request to the corresponding author.

Patient and public involvement

The local chiropractic patient and professional associations (Asociación Española de Usuarios de Quiropráctica and Asociación Española de Quiropráctica) have been involved throughout the study in the recruitment process and in promoting the trial. Upon completion of the study, the results will be disseminated to the patient community in the general assembly of the patient association, as per a formal agreement with the investigators.

Ethics and dissemination

This clinical trial obtained ethical approval by the Fundación Jiménez Díaz Clinical Research Ethics Committee. All participants in the study will sign an informed consent. Any amendment to the protocol will be communicated to the ethics review board

and the clinical trial registry. The results of the study will be submitted for publication in peer-reviewed journals and disseminated via scientific conferences and presentations directed to the professional and patient associations.

Discussion

The stratification of patients with CLBP is essential to better understand the needs of individual patients and provide targeted treatment. A mechanism-based classification is a promising avenue to match patients with the care that is best suited with their CLBP mechanism. However, there is an ongoing debate regarding the definition of these subgroups and the best available tools to diagnose them.[6 9 12 13] The most recent guidelines for the management of CLBP in both a primary care and a physiotherapy setting recommend SMT as one of the first options for care.[90 91] Nonetheless, it is not yet possible to identify which patients may benefit the most. The current study describes a protocol for a mechanistic randomised placebo-controlled trial that may contribute to unveil the CS-related mechanisms involved in CLBP relief by SMT. The main objective of the proposed trial is to provide some insight on potential mechanisms of SMT that may be particularly relevant for a subgroup of patients with CLBP. Grasping these mechanisms may help better guide conservative care for patients with CLBP by assessing clinical, neurophysiological, cognitive and/or biochemical variables at baseline.

Strengths and limitations

The main strength of the current study is the robust design using a validated placebo and assessing the blinding of participants, while ensuring the blinding of outcome assessors, statistician, laboratory technician and of the clinician delivering care to the patients' progress. This will substantially reduce potential biases that are typically

introduced in manual therapy trials. Additionally, the use of a control group will help determine reference values and their stability in a healthy population, which has not been readily reported, particularly concerning urinary levels of inflammatory cytokines.[61] Further to this, the multidimensional approach to defining central sensitization and the mechanisms leading to it may render relevant data in better defining pain mechanisms involved in CLBP.

Concerning the limitations of the study, the main one lies on the application of placebo or sham manipulations. Although SMT has been found to be as effective as other frequently used and recommended interventions for CLBP, it fails to outperform a placebo under highly controlled circumstances.[92] This is, however, an important limitation of most if not all back pain clinical trials.[93 94]

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Author contributions:

All authors contributed to the design of this protocol. CG-M and MP conceptualised and designed the protocol, except for every aspect related to laboratory analyses, which was conceptualised by AO-DM. The protocol was drafted by CG-M, and revised by MP and AO-DM. The statistical analysis was designed by MP. CG-M was responsible for ethical committee approval. All listed authors meet authorship criteria and have read and approved the final manuscript.

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Figure 2 was created with biorender.com

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Competing interests:

The authors have no conflict of interest and no commercial interest to declare.

Supplemental material:

The following documents are available as part of the supplemental material, in the Spanish language:

Supplemental appendix 1: Participant selection form

Supplemental appendix 2: Participant information sheet

Supplemental appendix 3: Informed consent form

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Figure legends

Figure 1. CONSORT diagrams of the randomized clinical trial proposed, including the healthy participants' control arm.

Figure 2. Study protocol for the clinical trial. The recruitment process is illustrated in figure 2–0, the collection of variable data during the initial examination is depicted with 2–1 and 2–2 (PPTs = Pressure Pain Thresholds). Figure 2–3 illustrates the treatment protocol (SMT = Spinal Manipulative Therapy) and Figures 2–4 and 2–5 the collection of variable data during the follow-up examination.

Figure 3. Quantitative sensory testing. Measurement of pressure pain thresholds (PPTs) and suprathreshold sensitivity with the use of a Wagner Force Dial FPX algometer at different body locations. **(A)** Local segmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment with the highest intensity clinical pain identified by the patient or via posterior to anterior manual palpation. **(B)** Dermatomal segmental PPTs measured over muscle tissue located under the dermatome of the segment identified in (A). **(C)** Heterosegmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment located four segments cranial to the segment identified in (A). **(D)** Remote segmental PPTs measured over muscle tissue in the centre of the thenar eminence.

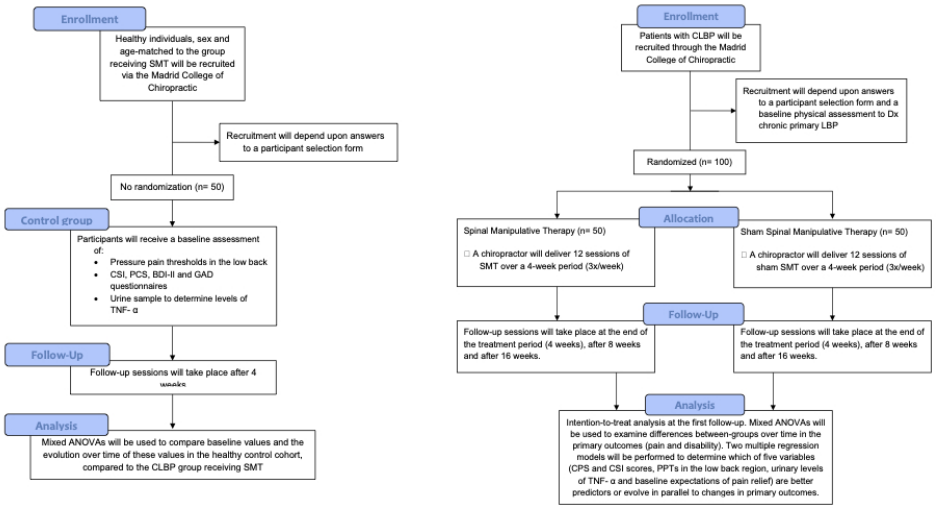

Figure 1. CONSORT diagrams of the randomized clinical trial proposed, including the healthy participants' control arm.

338x190mm (72 x 72 DPI)

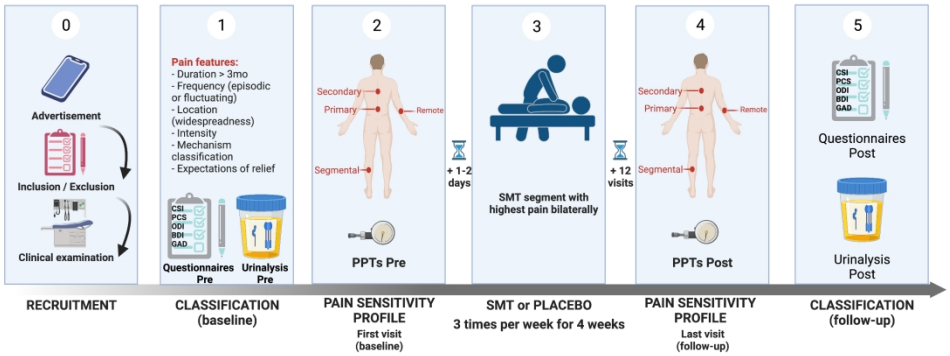

Figure 2. Study protocol for the clinical trial. The recruitment process is illustrated in figure 2–0, the collection of variable data during the initial examination is depicted with 2–1 and 2–2 (PPTs = Pressure Pain Thresholds). Figure 2–3 illustrates the treatment protocol (SMT = Spinal Manipulative Therapy) and Figures 2–4 and 2–5 the collection of variable data during the follow-up examination.

686x279mm (118 x 118 DPI)

Figure 3. Quantitative sensory testing. Measurement of pressure pain thresholds (PPTs) and suprathreshold sensitivity with the use of a Wagner Force Dial FPX algometer at different body locations. (A) Local segmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment with the highest intensity clinical pain identified by the patient or via posterior to anterior manual palpation. (B) Dermatomal segmental PPTs measured over muscle tissue located under the dermatome of the segment identified in (A). (C) Heterosegmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment located four segments cranial to the segment identified in (A). (D) Remote segmental PPTs measured over muscle tissue in the centre of the thenar eminence.

250x190mm (146 x 146 DPI)

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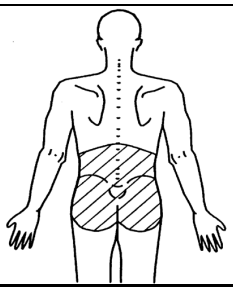
CUESTIONARIO PARA LA SELECCIÓN DE PARTICIPANTES

Nombre: Edad:

Número de teléfono:

Correo electrónico:

	Sí (especifique)	No
¿Padece Ud. de dolor lumbar en la zona indicada por el esquema, desde hace más de 3 meses? En caso afirmativo, ¿desde cuándo? 		
¿Sufre Ud. algún dolor de mayor intensidad o gravedad que el lumbar?		
¿Sufre Ud. dolor en sus manos/pulgares o en regiones cercanas a la lumbar?		
¿Ha sido Ud. diagnosticado con alguna enfermedad psiquiátrica o reumática?		
¿Toma Ud. algún medicamento regularmente para el dolor? ¿Cuál?		
¿Ha sido Ud. operado de la columna vertebral?		
¿Ha recibido Ud. tratamiento de manipulación vertebral en los últimos 12 meses?		
Si es Ud. mujer, ¿existe riesgo de estar embarazada?		

Firma del participante : _____ Fecha : _____

Firma del investigador : _____ Fecha : _____

REAL CENTRO UNIVERSITARIO
Escorial – María Cristina

DOCUMENTO INFORMATIVO RELATIVO AL DESARROLLO DEL PROYECTO DE INVESTIGACIÓN

TÍTULO DEL ESTUDIO	Eficacia de la terapia manipulativa quiropráctica en pacientes con lumbalgia crónica primaria: un estudio preliminar
CÓDIGO DEL ESTUDIO	EC113-21_FJD
PROMOTOR DEL ESTUDIO	Dr. Luis Álvarez Gálovich
INVESTIGADOR PRINCIPAL	Dra. Arantxa Ortega de Mues
CENTRO	Real Centro Universitario Escorial – María Cristina

INTRODUCCIÓN:

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por un Comité de Ética de la Investigación con medicamentos y por la Agencia Española de Medicamentos y Productos Sanitarios, de acuerdo a la legislación vigente, el Real Decreto 1090/2015 de 4 de diciembre y el Reglamento Europeo 536/2014 de 16 de abril, por los que se regulan los ensayos clínicos con medicamentos. Nuestra intención es que usted reciba la información correcta y suficiente para que pueda decidir si acepta o no participar en este estudio. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir. Además, puede consultar con las personas que considere oportuno.

Debe saber que su participación en este estudio es voluntaria y que puede decidir NO participar. Si decide participar, puede cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su atención sanitaria. No obstante, si participa en este estudio y nos permite evaluar su respuesta, nos estará ayudando a entender mejor los mecanismos asociados al dolor y a mejorar el tratamiento del dolor de espalda, a través de alternativas como la Quiropráctica.

Un grupo de investigadores del *Madrid College of Chiropractic* del Real Centro Universitario Escorial-Mª Cristina, la Fundación Jiménez-Díaz, la Universidad de Alcalá de Henares y la universidad de Quebec en Trois-Rivières (Canadá), está desarrollando un Trabajo de Investigación para cuyo desarrollo necesitan la participación de voluntarios con dolor lumbar crónico. Este trabajo formará parte de la tesis de doctorado de Carlos Gevers Montoro, que está cursando este programa en la Universidad de Montréal, también en Canadá. El presente documento contiene la información necesaria para que usted decida si quiere participar o no en este estudio.

PROCEDIMIENTO:

El objetivo de este estudio es el de investigar los efectos que tiene la manipulación quiropráctica sobre el dolor lumbar crónico. Para ello, mediremos una serie de variables clínicas relacionadas con su dolor, las características del mismo, su umbral y sensibilidad ante el dolor, y la presencia de unas moléculas relacionadas con la inflamación en su orina. Para el estudio hemos establecido 2 grupos, a los que serán asignados los participantes de manera aleatoria antes del inicio del estudio, con el objetivo de determinar si existen diferencias entre ellos. A un grupo se le aplicará una sesión de manipulación quiropráctica en la región lumbar, y al otro, una sesión de manipulación *placebo*. Ambos procedimientos son indistinguibles el uno del otro y se utilizan frecuentemente en la práctica clínica y en protocolos de investigación del mundo entero. Para este proyecto, necesitamos la participación de 100 adultos voluntarios, entre los 18 y 70 años.

Una vez determinado si usted puede participar en el estudio mediante el cuestionario de selección, se le citará para acudir a consulta con una muestra de orina tomada en ayunas, a la que se asignará un código numérico, y se le realizará una exploración física que confirmará que puede participar en el estudio. En caso afirmativo, se le solicitará que rellene tres cuestionarios relacionados con el dolor y se procederá a medir su umbral de dolor en varias regiones del cuerpo. Ese mismo día, se iniciará la primera sesión de tratamiento basado en dos manipulaciones en la columna vertebral. Ambas son inocuas y no presentan riesgos para su salud. Esta primera sesión durará unos 60-90 minutos.

Después de esta sesión, se planificarán las siguientes 11 sesiones, con una frecuencia de 3 sesiones por semana (total de 4 semanas). En las siguientes sesiones, se le realizarán una serie de preguntas cortas que responderá en el ordenador antes de realizar las manipulaciones. Todas las sesiones se desarrollarán de esta manera y tendrán una duración de unos 15-20 minutos, excepto la última sesión (número 12), en la cuál se le solicitará que acuda con una segunda muestra de orina, se volverán a medir los umbrales de dolor y se repetirán los cuestionarios completados en la primera sesión. Esta sesión durará cerca de los 60 minutos. Un mes después de la conclusión del estudio, nos pondremos en contacto con Ud. para hacerle una serie de preguntas cortas sobre su estado clínico. Para la organización de las sesiones, el coordinador del estudio estará en contacto con Ud. vía WhatsApp o e-mail, según su preferencia.

Sus únicas obligaciones son las de cumplir con las visitas y actividades del estudio, y notificar cualquier evento adverso que pueda experimentar en relación con el mismo. La participación no supondrá ningún coste para Ud., sino al revés, podría beneficiarle para su dolor. Las técnicas de manipulación que se emplearán en el estudio están recomendadas por guías de práctica clínica para el tratamiento del dolor lumbar. Los riesgos más habituales asociados a estas técnicas son la rigidez muscular, el aumento del dolor lumbar o molestias que irradian por la pierna, todas de carácter pasajero. El investigador encargado de realizar el tratamiento dispone de una póliza de seguros que se ajusta a la legislación vigente (Real decreto 1090/2015) y que le proporcionará la compensación e indemnización en caso de menoscabo de su salud o de lesiones que pudieran producirse en relación con su participación en el estudio, siempre que no sean consecuencia de la propia enfermedad que se estudia o de la evolución propia de su enfermedad como consecuencia de la ineficacia del tratamiento.

En caso de haber recibido la manipulación *placebo*, se le propondrá a continuación un tratamiento *real* de 4 semanas de duración (un total de 12 sesiones) sin ningún coste para Ud. En caso de haber recibido el tratamiento *real* durante el estudio, Ud. podrá decidir si continuar con el tratamiento quiropráctico una vez finalizado el estudio, asumiendo Ud. los cargos habituales.

Para evaluar los datos recogidos y tener en cuenta los factores que puedan influir en éstos, necesitaremos también recoger datos personales, como su edad o nivel de estudios además de tres cuestionarios, por lo que para participar en el estudio también tendrá que autorizarnos para poder consultar el historial clínico recogido en el Centro Quiropráctico, si fuera necesario además de permitirnos utilizar los datos recogidos en los cuestionarios, de forma totalmente anónima.

CONFIDENCIALIDAD:

En todo momento sus datos serán tratados con absoluta confidencialidad. Nadie ajeno al estudio tendrá acceso a los datos que recojamos, y esos datos nunca serán públicos de manera individual (es decir, nadie ajeno al estudio podrá saber qué datos corresponden específicamente a usted). Además, estos datos tampoco podrán ser usados para ningún fin distinto a los objetivos que este estudio persigue. Sus datos personales solo serán conservados en la base de datos del Centro Quiropráctico,

cuyo acceso está protegido bajo contraseña y restringido a las personas involucradas en su atención clínica. Los datos correspondientes al estudio estarán asociados a un código numérico que impedirá su identificación. Estos datos serán almacenados en formato físico y digital, en un archivador bajo llave y en un disco duro protegido mediante contraseña durante 25 años desde la conclusión del estudio. Solamente el investigador principal tendrá acceso a la totalidad de los datos. Las muestras de orina recogidas serán identificadas con el código del estudio y conservadas temporalmente en un frigorífico a -20ºC en el Centro Quiropráctico, para ser trasladadas posteriormente a la Universidad de Alcalá de Henares, lugar en el que serán analizadas y conservadas hasta la conclusión del estudio.

De acuerdo con el Reglamento General de Protección de Datos (Reglamento EU 2016/679), además de los derechos de acceso, rectificación, oposición y cancelación de datos, también tiene derecho a limitar el tratamiento de datos y solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar sus derechos, diríjase al investigador principal del estudio o al delegado de protección de datos (secretaria@rcumariacristina.com). Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho/a.

¿Para qué se utilizarán mis datos?
Sus datos son necesarios para mejorar el tratamiento no farmacológico del dolor lumbar, y en particular para el desarrollo y la introducción en el mercado de manera segura del tratamiento quiropráctico. Por lo tanto, se utilizarán según lo planeado en este estudio, así como dentro de las actividades de investigación relacionadas necesarias para estos objetivos con el fin de:

- comprender cómo funciona el tratamiento de manipulación vertebral y actuaciones similares,
- comprender mejor la lumbalgia crónica y los problemas de salud asociados,
- desarrollar pruebas de diagnóstico para la lumbalgia crónica
- aprender de estudios anteriores para planificar nuevos estudios,
- publicar los resultados de la investigación en revistas científicas o utilizarlos con fines educativos.

¿Cómo se comunicarán los resultados?
El promotor publicará el protocolo y los resultados del estudio a través del Registro Estadounidense www.clinicaltrials.gov. El promotor está obligado a publicar los resultados, tanto positivos como negativos, de los ensayos clínicos autorizados, preferentemente, en revistas científicas antes de ser divulgados al público no sanitario, con independencia de las obligaciones de publicación del informe de los resultados en el registro y de lo establecido al respecto en el Reglamento (UE) n.º 536/2014 del Parlamento Europeo y del Consejo, de 16 de abril de 2014.

PREGUNTAS: Si usted tiene preguntas acerca del procedimiento puede consultar en cualquier momento del estudio, antes, durante y después de su participación en el mismo, tanto con la persona que le ha entregado esta hoja informativa o dirigirse al responsable de su coordinación: Carlos Gevers Montoro (correo electrónico: cgevers@rcumariacristina.com ; teléfono de contacto: 644 439 221).

Habiendo leído el documento informativo y estando de acuerdo con los aspectos tratados en el mismo acepto participar en el Trabajo de Investigación "Eficacia de la terapia manipulativa quiropráctica en pacientes con lumbalgia crónica primaria: un estudio preliminar" y contribuir al desarrollo del mismo.

Firma del participante_____ Fecha_____

INVESTIGADOR PRINCIPAL: Dra. Arantxa Ortega de Mues aortega@rcumariacristina.com

REAL CENTRO UNIVERSITARIO
Escorial – María Cristina

CONSENTIMIENTO INFORMADO

NOMBRE Y APELLIDOS: _____

Código: _____ (no rellenar esta casilla)

"Eficacia de la terapia manipulativa quiropráctica en pacientes con lumbalgia crónica primaria: un estudio preliminar"

D/Dña. (nombre y apellidos)_____

Habiendo leído la hoja de información acerca del estudio,
Habiendo sido informado suficientemente de en qué va a consistir,
Habiendo preguntado y solucionado cuantas dudas tenía al respecto,

Participo voluntariamente en el mismo siempre y cuando:

1. Mis datos sean tratados de forma confidencial y solamente por parte de los profesionales que forman parte de la investigación.
2. Pueda retirarme del estudio en el momento en que así lo desee, sin dar explicaciones y sin que esto afecte a mi tratamiento ni a la atención sanitaria que reciba.
3. Pueda preguntar en cualquier momento cualquier duda acerca del desarrollo del estudio.

Cumpliéndose lo anteriormente dicho, participo libremente en el desarrollo de dicho estudio científico y acepto que mis datos sean usados en él.

Firma participante:_____ Fecha: _____

Firma investigador:_____ Fecha: _____

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 19-20
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	4,5
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12,13,15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13,14, Figs 1,2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8,12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16-17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17-18

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____13_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Included in consent form
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____16-17___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____20_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____16-17_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___13-14_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____17-18____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____N/A_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____17_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Consent form__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	In consent form

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Mechanisms of Chiropractic Spinal Manipulative Therapy for Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial

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Mechanisms of Chiropractic Spinal Manipulative Therapy for Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial

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Abstract

Introduction

Chronic low back pain (CLBP) is a highly prevalent and disabling condition. Identifying subgroups of patients afflicted with CLBP is a current research priority, for which a classification system based on pain mechanisms was proposed. Spinal manipulative therapy (SMT) is recommended for the management of CLBP. Yet, little data are available regarding its mechanisms of action, making it difficult to match this intervention to the patients who may benefit the most. It was suggested that SMT may influence mechanisms associated to central sensitisation. Therefore, classifying CLBP patients according to central sensitisation mechanisms may help predict their response to SMT.

Methods and analysis

This protocol describes a randomised placebo-controlled trial aiming to examine which variables linked to central sensitisation may help predict the clinical response to SMT in a cohort of CLBP patients. One hundred patients with chronic primary low back pain will be randomized to receive 12 sessions of SMT or placebo SMT over a 4-week period. Pain intensity will be assessed as the primary outcome after completing the 4-week treatment (primary endpoint), and at 4- and 12-week follow-ups. Baseline values of two pain questionnaires, lumbar pressure pain thresholds, concentrations of an inflammatory cytokine and expectations of pain relief will be entered as predictors of the response to SMT in a multiple regression model. Changes in these variables after treatment will also be used in a second multiple regression model. The reference values of these predictors will be measured from 50 age and sex-matched healthy controls to allow interpretation of values in patients. Mixed analyses of variance will also be conducted to compare the

primary and secondary outcome measures between groups (SMT vs. placebo) over time (baseline vs. post-treatment).

Ethics and dissemination: Ethical approval was granted by the Fundación Jiménez Díaz Clinical Research Ethics Committee.

Trial registration number: NCT05162924

Keywords: Randomized controlled trial; Low back pain; Patient stratification; Central Sensitization; Chiropractic Manipulation

Strengths and limitations of this study:

- This study will expand our understanding of the relevance of clinical, psychological, psychophysical and inflammatory variables in predicting the response of patients with chronic low back pain to manual therapy.
- The design including a control group with healthy participants will allow confirming the usefulness of a classification system for patients with chronic primary low back pain according to the underlying pain mechanisms.
- The blinding of outcome assessors, statistician, laboratory technician, and of the investigator providing care to the patients' progress will contribute to reduce bias.
- A high degree of similarity between the sham and real manipulations increases the odds of successfully blinding participants. However, the sham intervention may produce clinical effects.
- Clinical trials on manual therapy, including the present study, are limited by the impossibility of blinding the investigator providing care to the intervention.

Introduction

Low back pain (LBP) is the single most important cause of disability globally,[1] with a high proportion of patients whose pain persists or recurs.[1-4] Aiming to identify patient profiles that respond more favourably to specific treatments and their prognosis, recent investigations highlight the importance of identifying subgroups among people with chronic LBP (CLBP). One of the proposed classification systems stratifies patients into specific subgroups according to pain mechanisms (nociceptive, neuropathic or central sensitisation).[5-10] It has been suggested that a large proportion of CLBP patients presents chronic primary pain, which has been linked to altered nociceptive processing.[11 12] Among the phenomena that may underlie this aberrant processing, central sensitization (CS) is likely the predominant mechanism,[12 13] and its involvement in CLBP deserves further research.[14]

One of the currently recommended interventions for the management of CLBP is spinal manipulative therapy (SMT).[15 16] However, not all patients have an identical response.[17] There is insufficient data to determine which CLBP subgroups respond better to this intervention.[18 19] This may be so because the analgesic mechanisms are still largely unknown. It was proposed that the pain relieving effects of SMT partly rely on segmental pain inhibition processes.[20] These processes influence temporal summation of pain,[21 22] primary, and secondary hyperalgesia,[23 24] which may be measured to identify patients with a CS phenotype. Further, emerging data from animal and human studies support the hypothesis that SMT modulates the inflammatory response, influencing inflammatory cytokines.[25-28] Cytokines can induce neuroinflammation, which may mediate the development of CS[29 30] in the transition towards chronic pain.[8 31] SMT may thus relieve CLBP by impacting mechanisms linked to CS.[24 32-34]

Altered pain sensitivity in a specific musculoskeletal region may indicate nociplastic pain,[12 35 36] likely reflecting CS.[13] Abundant studies have reported that a subgroup of CLBP patients demonstrate segmental mechanical hyperalgesia, assessed via lower pressure pain thresholds (PPTs) in low back or lower extremity areas, when compared to healthy controls.[37-42] Changes in pain sensitivity are not confined to lumbar segments but rather may be present in remote anatomical locations.[14 38 43-45] Increased pain sensitivity is a clinical indicator possibly reflecting CS not just at the spinal level, but potentially implicating supraspinal structures.[8 14 31] Thus, it is plausible that mechanical pain sensitivity may play an important role in defining a CS phenotype in CLBP.[35]

Pain catastrophising has been described as a psychological trait and pain cognition linked to the development of CLBP with an altered pain sensitivity profile and a CS phenotype.[46-48] CLBP patients with higher pain sensitivity often demonstrate higher levels of catastrophising and other negative psychological traits[32 49-51] Similarly, higher pain catastrophising was associated with higher central sensitization inventory (CSI) scores.[52] The CSI and a clinical presentation suggestive of CS mechanisms has been proposed to identify a specific CLBP subgroup.[5 6 53 54]

Currently, the mechanisms leading to CS are still unknown, however, recent data suggest an important role for neuroinflammation.[29] Neuroinflammation may act at multiple levels, from the periphery[50] to the brain,[55] including the dorsal horn of the spinal cord.[56] The release of inflammatory cytokines, including the pro-inflammatory tumour necrosis factor alpha (TNF-α), was identified as a potential mechanism supporting this phenomenon.[29 30 57 58] Studies have shown an association between proinflammatory cytokines and CLBP,[59-62] suggesting that these may serve as a reliable biomarker to identify patients with a CS phenotype.

The classification of mechanism-based pain phenotypes is a complex and controversial task,[35 63 64] for which a variety of clinical, inflammatory, psychological, and psychophysical constructs must be considered.[9 65] Although CS may influence changes in pain sensitivity induced by SMT,[32] pain phenotyping has been scarcely applied to manual therapy research.[66] Therefore, the response of this subgroup of patients to SMT has yet to be assessed. The aim of this clinical trial is to investigate whether variables associated with a CS phenotype may help predict the response to SMT. The specific objectives are: 1) to identify the clinical, psychological, psychophysical and inflammatory variables linked to CS in a cohort of CLBP patients; and 2) to examine which of these variables predict the clinical response to SMT.

Methods

Experimental design and setting

The study consists of a mechanistic randomized placebo-controlled clinical trial with a mixed experimental design, whose objective is to assess which variables linked to CS in chronic pain patients can predict the response of CLBP patients to SMT (Figure 1). This protocol is reported according to the guidelines for clinical trial protocols Standard Protocol Items: Recommendations for Interventional Trials[67] (SPIRIT statement). Starting in November 2021, 150 participants will be recruited through the Madrid College of Chiropractic (MCC) teaching clinic in San Lorenzo de El Escorial (Spain). This includes 100 patients with CLBP and 50 healthy participants. The MCC clinic is a primary care setting specialized in spine care, including chiropractic and physical therapy services. Clinical, psychological, psychophysical and inflammatory variables will be measured in CLBP patients, which will be exposed to either SMT or a placebo SMT for 12 visits over a 4-week period. A group made up of 50 age and sex-matched healthy

volunteers will be used to determine the reference values of the same psychological, psychophysical, and inflammatory variables in a healthy population and compare them with the clinical population, before and after exposure.

Selection criteria

An investigator with over twenty years of clinical experience will be responsible for the selection of participants. To be eligible to participate in the study, patients must be 18 to 70 years old, receive a diagnosis of chronic primary LBP of at least 3-month duration, with or without leg pain (according to a clinical examination carried out at the MCC). If pain affecting the low back or lower limb is suspected to be predominantly of neuropathic origin, the patient will be excluded.[12] Additionally, patients will be excluded from the study if they present any of the following criteria: evidence of specific pathology as the cause of their CLBP, diagnosis of mental illness (with the exception of anxiety and depression, as these conditions are frequently comorbid with CLBP[68 69] and may suggest a CS phenotype[5 49]), presence of pain of equal or higher intensity affecting any other body region, use of corticosteroids, opiates or anti-cytokine medication, pregnancy, lumbar fusion surgery or recent laminectomy, having received chiropractic SMT in the 12 months prior to the beginning of the study.[5 50 51]

A cohort of healthy volunteers will be recruited to be used as a reference for the psychological, psychophysical, and inflammatory variables collected in the sample of CLBP patients. They will be age- and sex-matched to the patients allocated to the group receiving SMT. Individuals meeting the following criteria are eligible to participate: being 18 to 70 years old; presenting no current or chronic pain condition, as well as not having received any diagnosis of a systemic, inflammatory, neurological or psychiatric condition.

Randomisation, concealed allocation, and blinding

A computer application (random-number generator) will be used to generate a balanced randomisation sequence. Participants will be allocated in a 1:1 ratio to the intervention (SMT) or placebo arms following the chronological order of recruitment. Patients, outcome assessors and statistician will be blinded to group allocation. To confirm the efficacy of the patients' blinding, participants will respond in three occasions to the questions: "Do you think that the treatment you have received is a real chiropractic treatment for back pain?"; and "On a numerical rating scale of 0–100, please rate the degree of certainty for having received a real chiropractic treatment" (with 0 being total uncertainty and 100 being absolute certainty).[70]

Additionally, to avoid biases in the reporting of patient-reported outcome measures and to blind the investigator delivering the interventions, participants will provide these data via electronic questionnaires without the presence or interference of any investigator.

Interventions

Both real and placebo SMT will be delivered by a chiropractor with twenty years of experience that is part of the research team (CG-M). Two real SMT will be performed with the patient positioned in the lateral decubitus position (once on each side), by applying a high-velocity, low-amplitude force on the manipulated segment, with the aim of generating at least one joint cavitation (associated with an audible sound). For this, the chiropractor will use the hypothenar surface or the last phalanx of the 2nd and / or 3rd fingers of the hand to contact the spinous process of the vertebral segment with the most intense clinical pain (see supplemental Figure S1A), as detected in the initial patient

examination. In case of not perceiving a cavitation or satisfactory joint movement, SMT may be repeated once on each side. Therefore, all participants will receive a minimum of two and a maximum of four SMT thrusts. Participants in the placebo arm will receive a validated sham SMT that is very similar to SMT.[70] The patient is positioned in the same lateral decubitus position, with the lower leg in extension and the upper leg in flexion, and an unintended force is applied bilaterally to the gluteal region (Figure S1B). The number of real or placebo SMT attempts resulting in joint cavitation will be recorded. Participants in both groups will receive 3 treatment session per week for 4 weeks (see Figure 2D). Healthy volunteers will receive no intervention during the same timeframe of 4 weeks (see Figure 3).

Outcome variables

Primary outcome

Patients will rate their current CLBP intensity, as well as the average, minimum and maximum pain throughout the preceding seven days or since the time of the previous session, once the study is underway,[71 72] using a numerical rating scale between 0 (no pain) and 100 (maximum pain imaginable). Average pain intensity will be used as the primary outcome for all statistical analyses. The primary endpoint will be the change from baseline at the completion of the 12 sessions of SMT. For the follow-up, average pain intensity will be assessed 4 and 12 weeks after the completion of the trial.

Secondary outcomes

Five topics were identified to discriminate pain mechanisms between groups of patients, including CS mechanisms: clinical examination, questionnaires, quantitative sensory testing, laboratory tests, and imaging tests [9]. For the present study, all categories

will be considered except the last one, which will only be used to rule out pain of suspected neuropathic or nociceptive aetiology. Variables belonging to these categories will be assessed for exploratory purposes and five of them will be examined as predictors of the response to SMT (two questionnaires, one quantitative sensory testing variable, one laboratory test variable and the expectations of pain relief).

Clinical examination variables

Data on the characteristics of the patients' CLBP will be collected at baseline for exploratory purposes: CLBP trajectory (duration and frequency) and localization. The duration of CLBP will be calculated as the number of months since the onset of the first episode of LBP. As for pain frequency, participants' CLBP trajectory will be classified as either fluctuating or episodic, depending on whether they recall asymptomatic periods of at least 4 weeks (episodic) or not (fluctuating).[73] For pain localization, patients will also draw the area affected by their pain on a tablet, using an application (Symptom Mapper) that will allow to calculate the degree of pain widespreadness.[74]

Additionally, CLBP will be classified as either proportionate or disproportionate to the degree or nature of the injury or pathology, with a discrete or diffuse distribution, according to criteria that were defined in the literature.[5 6] A diffuse rather than a discrete pain distribution was identified as a key criterion of a CS phenotype.[5 12] Also, classifying symptoms as proportionate (or not) was proposed to differentiate nociceptive pain from CS mechanisms.[35] The pattern of pain distribution and the provocation and response to aggravating and palliative factors will be assessed during case history and physical examination. This will be complemented with information provided by diagnostic imaging when available.[9]

Finally, other variables will be reported such as the intake of pain medication compatible with the selection criteria, both at baseline and at after treatment. Similarly,

whether the patient regularly smokes will be documented, since smoking has been associated with increased serum levels of pro-inflammatory cytokines.[75] The average number of hours of sleep will also be recorded, as it may help predict pain patterns.[76] Additionally, the presence of any chronic condition (including pain) that are comorbid with the CLBP will be recorded for exploratory purposes.

Questionnaire variables

The main secondary outcome will be the disability caused by CLBP. After completing the case history, patients will fill out the Oswestry low back disability index questionnaire.[77] The questionnaire will also be completed after the 12th treatment session with the primary endpoint, and at subsequent 4- and 12-week follow-ups.

The Pain Catastrophizing Scale (PCS) and CSI will be completed before the beginning of the treatment (baseline) and at a single follow-up after the 12th treatment session.[78 79] The PCS will be used to identify specific pain cognitions that are frequently present in patients with a CS phenotype, this measure will be used to evaluate the association of CLBP with psychosocial factors described by Smart et al.[5] When combined with a clinical presentation suggestive of CS,[35] the CSI is an useful tool to identify patients compatible with certain CS mechanisms, particularly when using the cut-off value of 40 points.[80] Both these scores will be examined as predictors due to their intrinsic association with a CS phenotype.

In addition, the Beck Depression Inventory II (BDI-II) and the Generalized Anxiety Disorder scale (GAD) questionnaires will be used to screen and quantify symptoms of depression and anxiety.[81 82] The scores in these questionnaires will be measured both at baseline and after the 12th treatment session for exploratory purposes. We will examine whether these variables are associated with the primary outcome. Pre

and post reference values of all questionnaires (PCS, CSI, BDI-II and GAD) will be taken from the healthy control participants in the same timeframe (Figure 3).

Quantitative sensory testing variables

Quantitative sensory testing based on the German protocol[83 84] will be performed with the aim of evaluating pain thresholds and sensitivity (see Figure 2C). Testing will consist of the exploration of the PPTs in deep tissues (Figure 4), using an algometer (Wagner Force Dial FPX, Greenwich, CT, USA). In addition, patients will rate the intensity of the first stimulus above threshold, using a numerical rating scale 0–100.[85] PPTs will be assessed by two interns completing their Master's in Chiropractic degree, after three months of training and pilot data collection. One of the two outcome assessors will be randomly assigned to each patient to perform both baseline and follow-up measurements. Two measurements will be taken bilaterally at a rate of about 50 kPa/s, and the arithmetic mean of both the thresholds and sensitivities reported calculated. Two consecutive measurements provide excellent reliability when assessing both populations with and without LBP,[86 87] while performing two repetitions per side of the lower back was proposed to optimize inter-session reliability.[88] PPTs will be performed over muscle tissue in 4 different locations. Primary pain will be assessed 2.5 cm lateral to the spinous process in the erector spinae[85] of the vertebral segment with the highest clinical pain intensity indicated by the patient and verified by palpation (Figure 4). Manual palpation will be performed to confirm that the selected segment either reproduces clinical pain or is the closest to the area (or to the centre) of CLBP symptoms. This will allow to assess the area of primary pain or hyperalgesia (segmental sensitivity). In addition, PPTs will be measured on both lower limbs in the dermatome corresponding to the segment of highest clinical pain intensity (dermatomal sensitivity), in the erector spinae four to six segments cranial to the most painful lumbar segment (heterosegmental sensitivity in a non-

symptomatic segment: secondary hyperalgesia), and in a remote location in both thenar eminences (widespread sensitivity). PPTs will be assessed during the initial examination for baseline and after the final treatment session (see Figures 2C and 2E). Reference values will be taken in healthy volunteers in the same locations as the CLBP participants receiving SMT (lumbar segmental, dermatomal, heterosegmental, widespread) at baseline and after 4 weeks (Figure 3).

Laboratory test variables: TNF-α as an inflammatory biomarker in urine

Before initiating the first treatment session and on the day of the last treatment session, urine samples will be collected (first morning micturition) and stored at -20º C (see Figure 2B and 2F). Additionally, the first morning micturition will be collected twice from healthy individuals in the same timeframe (two samples with a 4-week delay, see Figure 3).[62] Samples will be deidentified by using only the participant's ID code, and the laboratory technicians will be blinded to group allocation. Urine concentrations of tumour necrosis factor alpha (TNF-α) will be quantified for each sample using specific ELISA for TNF-α following manufacturer's instructions. The cytokine to creatinine ratio will be calculated to correct for differences in urine volumes.[89] TNF-α values, including urinary concentrations, were found to be elevated in CLBP patients and may respond to a treatment based on SMT.[25 27 59 62 90]

Expectations

Before initiating treatment, each participant will be asked to rate their expectations of pain relief upon completion of the study. To do this, a verbal evaluation will be provided using a visual analogue scale with the descriptors -100, equivalent to "total pain relief," 0, equivalent to "no change," up to +100, equivalent to "maximum pain increase". Such an assessment of patients' expectations allows to identify their contribution as part

of the placebo response, which were found to predict the response to treatment for chronic pain.[91]

Adverse events reporting

At the beginning of every SMT or placebo treatment sessions, patients will inform whether they have suffered any adverse effects that they feel could be related to the treatment received via an electronic questionnaire. Adverse effects will be classified into four categories most frequently reported after lumbar SMT as identified in a clinical trial: muscle stiffness, increased pain, radiating discomfort, and others.[92] In addition, patients will indicate whether they were triggered immediately, up to 24 hours, or more than 24 hours after the previous session, whether their duration was of minutes, hours (< 24 hours), between 24 and 48 hours, or longer than 48 hours,[92] and according to their intensity (very mild, mild, moderate, severe, very severe). The reporting of adverse events will be monitored by an investigator not involved in clinical care or examination. A 30-point increase in pain intensity or the reporting of moderate to severe adverse events in three consecutive visits will raise the alarm and the patient will be interviewed to determine whether care should be interrupted.

Healthy volunteers will be contacted one week prior to the follow-up appointment to rule out any of the following criteria that would exclude them from the follow-up: presence of pain or other symptoms for > 7 days, trauma or injury, initiating a new treatment or receiving a diagnosis compatible with the exclusion criteria. In addition, if the participant reports any pain or taking any pain medication within 24 hours of the follow-up, this session will be postponed for up to one week.

Procedures

Candidates interested in participating in the study will initially complete a form with the selection criteria (Supplemental Appendix 1). If the criteria are met, patients will schedule an appointment at the MCC clinic where they will read and sign a participant information sheet, and the informed consent (Supplemental Appendices 2 and 3). Subsequently, patients will undergo a clinical examination (consisting of a case history and physical examination) to confirm the diagnosis of chronic primary LBP, during which all outcomes will be collected, except for the urine sample that will be provided before the first treatment session. Patients will then participate in 12 treatment sessions divided into three weekly sessions for 4 weeks. All outcome measures will be re-assessed at the 12th and last treatment session (i.e., the primary endpoint). After completing data collection at the primary endpoint, patients allocated to the placebo arm will be offered the possibility of receiving the "real" SMT, free of charge, at the MCC. In addition, all patients will be contacted for the follow-up of CLBP intensity and disability, 4 and 12 weeks after the primary endpoint (Figure 2G). Meanwhile, healthy volunteers will participate in two visits (baseline and follow-up after 4 weeks) when all relevant outcomes will be assessed (Figure 3). The study will have a total estimated duration of one year.

Sample size calculation

To determine the ideal number of participants, the second aim to identify the variables linked to a CS phenotype that could help predict the response to treatment based on SMT for CLBP was considered. A multiple regression analysis will be performed using five independent variables described in the statistical analysis section as predictors. These variables include baseline values of local PPTs, urinary concentrations of TNF, scores in PCS and CSI questionnaires and a priori expectations of pain relief. For each

predictor variable, it is recommended to estimate about 10 sample elements, therefore we predict that a sample size of 50 patients per group will be necessary.[93] A total of 110 patients will be recruited, accounting for an estimated dropout rate of 5-10%.

Regarding the primary outcome variable (pain intensity), a reduction in pain intensity after one month in patients who receive 12 sessions of SMT compared to placebo will be expected. We aim to detect small to moderate effects since it is a one-month intervention in patients with chronic pain unresolved by other treatments over at least 3 months. Therefore, based on an effect size of f = 0.175, an alpha of 0.05, a power of 0.8 for 2 groups and 2 repeated measures (baseline and primary endpoint), and a correlation between the repeated measures of 0.5, the size of the necessary sample is 34 patients per group, thus a total of 68 patients to detect statistically significant changes in clinical pain and disability. Therefore, the analysis based on the regression model to predict the clinical course provides with a large enough size for identifying small between-group differences.

Statistical analysis

The normal distribution of the data will be verified using the Kolmogorov-Smirnov test. Data deviating from normality will be transformed to obtain a normal distribution before being entered into the data analysis. In order to interpret the values in outcomes measured in patient groups, these will be compared with reference values obtained from the healthy controls to the CLBP group receiving SMT. This will allow characterizing the patients' groups (aim 1) to determine whether they show increased psychological symptoms, pain sensitivity and hyperalgesia as well as increased TNF-α levels compared with a reference healthy population. A series of mixed analyses of variance (ANOVA) will be performed to examine differences in PPTs, urinary TNF-α levels, PCS, CSI, BDI-II and GAD scores before and after the 4-week treatment period

between the three groups (control, SMT and placebo). To test a priori hypotheses, significant effects will be decomposed using planned comparisons. For the rest of the effects, Tukey's HSD will be used for testing any pairwise comparisons between group means.

Pearson's product-moment correlation analyses will be carried out to examine the association between the primary and secondary variables that demonstrate significant effects between groups over time. Subsequently, two multiple regression models will be used to examine the predictors of improvement in clinical pain and disability over time in patients who have received SMT (aim 2). The variables used as predictors for this analysis will be: baseline PCS and CSI score, baseline PPTs in the primary pain region, baseline TNF-α levels, and (baseline) expectations of pain relief. In addition, in another regression model, the changes (delta) in these variables (except expectations of pain relief, which are only measured a priori) after 4 weeks of treatment will be used as predictor variables. This is done to identify the variables most associated with clinical evolution to answer the mechanistic question.

The primary outcome variable (clinical pain intensity) will be compared between groups (SMT vs. placebo) over time at the primary endpoint using a mixed ANOVA. Average pain intensity since the last treatment visit and in the seven days prior to the initial visit will be the variable used for statistical analyses. With an exploratory objective, the secondary variables (disability-ODI, PCS, CSI, BDI-II, GAD scores, PPTs, degree of pain widespreadness, urinary cytokine levels, number and severity of reported adverse effects, presence of leg pain, pain medication use) will be compared between groups (SMT vs placebo) over time (baseline and post-treatment) using mixed ANOVAs. To test a priori hypotheses, significant effects will be decomposed using planned comparisons.

For the rest of the effects, Tukey's HSD will be used for testing any pairwise comparison between group means.

As recommended by White et al., efforts will be directed towards following up all participants for every time point.[94] An intention-to-treat analysis including all randomized study participants with a baseline endpoint assessment will be performed. The use of mixed model ANOVA allows to include all study participants with a lower attrition bias,[95] while handling missing data using maximum likelihood estimations. Further, a per-protocol analysis will be also performed excluding study participants who voluntarily drop out from the study, develop a severe adverse reaction (increase in >30 points average pain intensity associated to treatment) or fail to attend three consecutive visits, or more than two treatment weeks. Finally, in order to test whether the data is not missing at random, a sensitivity analysis will be conducted to explore the effect of attrition [94].

Data management and monitoring

All data will be collected at the MCC teaching clinic of the Real Centro Universitario María Cristina. The clinic utilizes a password-protected computer app that generates a patient file number linked to their clinical and personal data. This file number will be connected to a unique participant ID code made up of three numbers and a letter. This ID code will be used to deidentify all clinical trial data. Only the investigator involved in delivering care will have knowledge of which clinic file number corresponds to which study ID code. The participants' selection, information, consent forms and outcome measures collected in paper format will be securely stored in a file cabinet at the MCC clinic. Patient-reported outcome measures will be collected electronically using the study ID code to complete a google form (Google Inc.). Both paper and online data will

be transferred to a password-protected spreadsheet, only accessible to the principal investigator. Data will be stored deidentified for 25 years after final publication. The dataset will be made available after publication of the trial, upon request to the corresponding author.

Patient and public involvement

The local chiropractic patient and professional associations (Asociación Española de Usuarios de Quiropráctica and Asociación Española de Quiropráctica) have been involved throughout the study in the recruitment process and in promoting the trial. Upon completion of the study, the results will be disseminated to the patient community in the general assembly of the patient association, as per a formal agreement with the investigators.

Ethics and dissemination

This clinical trial obtained ethical approval by the Fundación Jiménez Díaz Clinical Research Ethics Committee. All participants in the study will sign an informed consent. Any amendment to the protocol will be communicated to the ethics review board and the clinical trial registry. The results of the study will be submitted for publication in peer-reviewed journals and disseminated via scientific conferences and presentations directed to the professional and patient associations.

Discussion

The stratification of patients with CLBP is essential to better understand the needs of individual patients and provide targeted treatment. A mechanism-based classification is a promising avenue to match patients with the care that is best suited with their CLBP

mechanism. However, there is an ongoing debate regarding the definition of these subgroups and the best available tools to diagnose them.[6 12 35 63 64] The most recent guidelines for the management of CLBP in both a primary care and a physiotherapy setting recommend SMT as one of the first options for care.[96 97] Nonetheless, it is not yet possible to identify which patients may benefit the most. The current study describes a protocol for a mechanistic randomised placebo-controlled trial that may contribute to unveil the CS-related mechanisms involved in CLBP relief by SMT. The main objective of the proposed trial is to provide some insight on potential mechanisms of SMT that may be particularly relevant for a subgroup of patients with CLBP. Grasping these mechanisms may help better guide conservative care for patients with CLBP by assessing clinical, neurophysiological, cognitive and/or biochemical variables at baseline.

Strengths and limitations

The main strength of the current study is the robust design using a validated placebo and assessing the blinding of participants, while ensuring the blinding of outcome assessors, statistician, laboratory technician. Moreover, the investigator delivering care will be blinded to the patients' progress. This will reduce biases that are typically introduced in manual therapy trials. Additionally, the use of a control group will help determine reference values and their stability in a healthy population, which has not been readily reported, particularly concerning urinary levels of inflammatory cytokines.[62] Further to this, the multidimensional approach to defining central sensitization and the mechanisms leading to it may render relevant data in better defining pain mechanisms involved in CLBP.

Regarding potential limitations, having only one clinician may limit the generalizability of the SMT effects. However, it also has the advantage of standardizing

the interventions and reducing variability in the procedures. It should also be noted that, although blinding the investigator providing care is desirable, it is impossible in manual therapy trials[98], including the present study. As the sham and real SMT have a high degree of similarity, effective blinding of participants is feasible.[70] The inability to distinguish the placebo from the real treatment is desirable to limit interpretation bias, particularly in a mechanistic trial as in the present study.[99] However, the sham SMT may rely on specific mechanisms that overlap with those of real SMT, leading to treatment effects.[99 100] Accordingly, the sham SMT should not be considered as an inert placebo and the lack of between-group differences should be interpreted with caution, with a potential risk for type II errors.

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Author contributions:

All authors contributed to the design of this protocol. CG-M and MP conceptualised and designed the protocol, except for every aspect related to laboratory analyses, which was conceptualised by AO-DM. The protocol was drafted by CG-M, and revised by MP and AO-DM. The statistical analysis was designed by MP. CG-M was responsible for ethical committee approval. All listed authors meet authorship criteria and have read and approved the final manuscript.

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Competing interests:

The authors have no conflict of interest and no commercial interest to declare.

Supplemental material:

The following documents are available as part of the supplemental material, in the Spanish language:

Supplemental figure S1: Photographs depicting the real (S1A) and sham (S1B) spinal manipulative therapy procedures.

Supplemental appendix 1: Participant selection form

Supplemental appendix 2: Participant information sheet

Supplemental appendix 3: Informed consent form

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Figure legends

Figure 1. CONSORT diagrams of the randomized clinical trial proposed, including the healthy participants' control arm.

Figure 2. Study protocol for the clinical trial. The recruitment process is illustrated in figure 2A, the collection of variable data during the initial examination is depicted with 2B and 2C (PPTs = Pressure Pain Thresholds). Figure 2D illustrates the treatment protocol (SMT = Spinal Manipulative Therapy) and Figures 2E and 2F the collection of variable data at the end of the 4-week treatment (i.e., primary endpoint), and Figure G the collection of pain intensity and disability data at the 4- and 12-week follow-ups.

Figure 3. Study protocol for the healthy control arm. The recruitment process is illustrated in 3A, the collection of variable data during the initial examination is depicted with 3B and 3C (PPTs = Pressure Pain Thresholds). Participants will receive no treatment (3D) and variable data will collected after four weeks for follow-up (3E and 3F).

Figure 4. Quantitative sensory testing. Measurement of pressure pain thresholds (PPTs) and suprathreshold sensitivity with the use of a Wagner Force Dial FPX algometer at different body locations. **(A)** Local segmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment with the highest intensity clinical pain identified by the patient or via posterior to anterior manual palpation. **(B)** Dermatomal segmental PPTs measured over muscle tissue located under the dermatome of the segment identified in (A). **(C)** Heterosegmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment located four segments cranial to the segment identified in (A). **(D)**

Remote segmental PPTs measured over muscle tissue in the centre of the thenar eminence.

Supplemental figure S1: Photographs depicting the real (S1A) and sham (S1B) spinal manipulative therapy procedures.

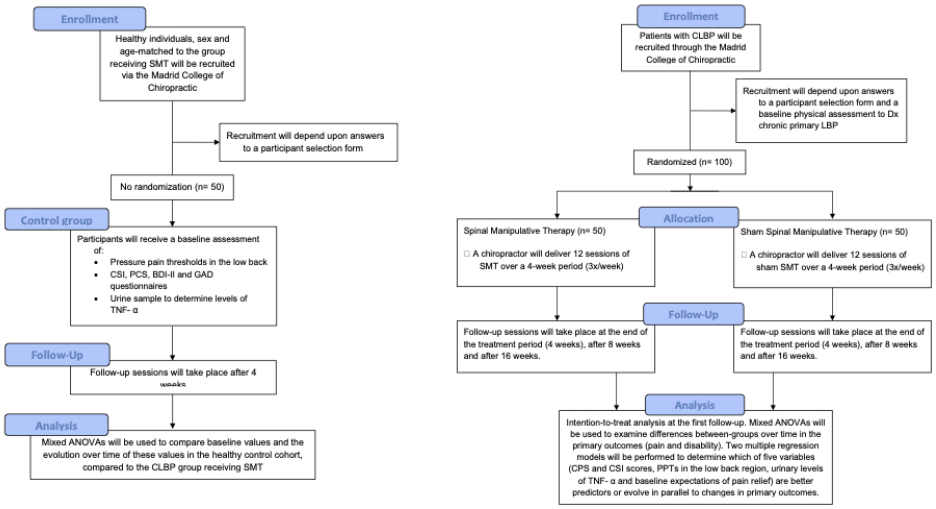
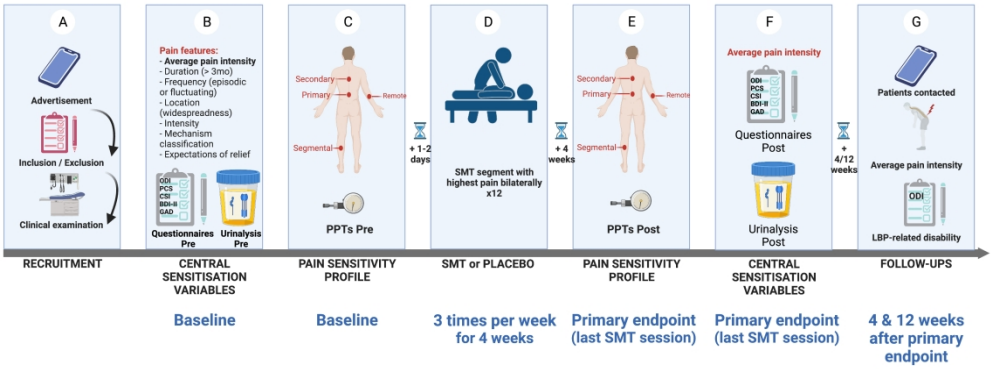


Figure 1. CONSORT diagrams of the randomized clinical trial proposed, including the healthy participants' control arm.

338x190mm (72 x 72 DPI)



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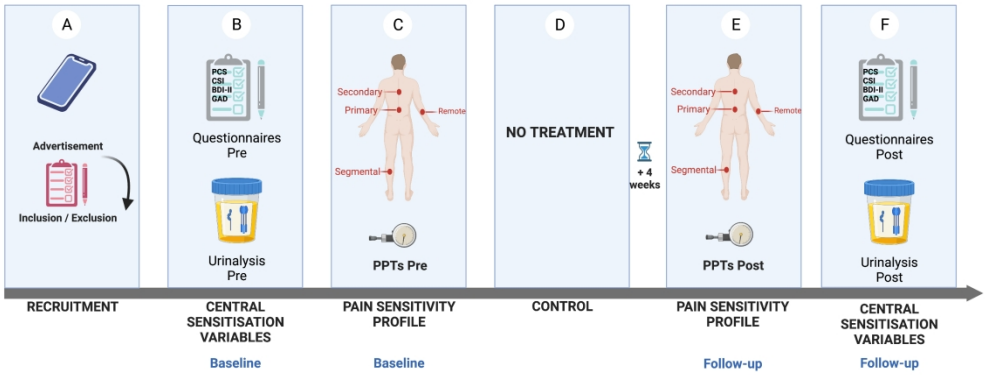
307x116mm (300 x 300 DPI)



Study protocol for the healthy control arm. The recruitment process is illustrated in 3A, the collection of variable data during the initial examination is depicted with 3B and 3C (PPTs = Pressure Pain Thresholds). Participants will receive no treatment (3D) and variable data will collected after four weeks for follow-up (3E and 3F).

266x103mm (300 x 300 DPI)

Figure 4. Quantitative sensory testing. Measurement of pressure pain thresholds (PPTs) and suprathreshold sensitivity with the use of a Wagner Force Dial FPX algometer at different body locations. (A) Local segmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment with the highest intensity clinical pain identified by the patient or via posterior to anterior manual palpation. (B) Dermatomal segmental PPTs measured over muscle tissue located under the dermatome of the segment identified in (A). (C) Heterosegmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment located four segments cranial to the segment identified in (A). (D) Remote segmental PPTs measured over muscle tissue in the centre of the thenar eminence.

250x190mm (146 x 146 DPI)

Supplemental figure S1: Photographs depicting the real (S1A) and sham (S1B) spinal manipulative therapy procedures.

528x351mm (72 x 72 DPI)

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CUESTIONARIO PARA LA SELECCIÓN DE PARTICIPANTES

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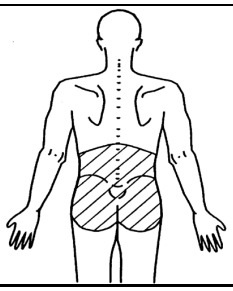
Número de teléfono:

Correo electrónico:

	Sí (especifique)	No
¿Padece Ud. de dolor lumbar en la zona indicada por el esquema, desde hace más de 3 meses? En caso afirmativo, ¿desde cuándo? 		
¿Sufre Ud. algún dolor de mayor intensidad o gravedad que el lumbar?		
¿Sufre Ud. dolor en sus manos/pulgares o en regiones cercanas a la lumbar?		
¿Ha sido Ud. diagnosticado con alguna enfermedad psiquiátrica o reumática?		
¿Toma Ud. algún medicamento regularmente para el dolor? ¿Cuál?		
¿Ha sido Ud. operado de la columna vertebral?		
¿Ha recibido Ud. tratamiento de manipulación vertebral en los últimos 12 meses?		
Si es Ud. mujer, ¿existe riesgo de estar embarazada?		

Firma del participante : _____ Fecha : _____

Firma del investigador : _____ Fecha : _____

REAL CENTRO UNIVERSITARIO
Escorial – María Cristina

DOCUMENTO INFORMATIVO RELATIVO AL DESARROLLO DEL PROYECTO DE INVESTIGACIÓN

TÍTULO DEL ESTUDIO	Eficacia de la terapia manipulativa quiropráctica en pacientes con lumbalgia crónica primaria: un estudio preliminar
CÓDIGO DEL ESTUDIO	EC113-21_FJD
PROMOTOR DEL ESTUDIO	Dr. Luis Álvarez Gálovich
INVESTIGADOR PRINCIPAL	Dra. Arantxa Ortega de Mues
CENTRO	Real Centro Universitario Escorial – María Cristina

INTRODUCCIÓN:

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por un Comité de Ética de la Investigación con medicamentos y por la Agencia Española de Medicamentos y Productos Sanitarios, de acuerdo a la legislación vigente, el Real Decreto 1090/2015 de 4 de diciembre y el Reglamento Europeo 536/2014 de 16 de abril, por los que se regulan los ensayos clínicos con medicamentos. Nuestra intención es que usted reciba la información correcta y suficiente para que pueda decidir si acepta o no participar en este estudio. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir. Además, puede consultar con las personas que considere oportuno.

Debe saber que su participación en este estudio es voluntaria y que puede decidir NO participar. Si decide participar, puede cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su atención sanitaria. No obstante, si participa en este estudio y nos permite evaluar su respuesta, nos estará ayudando a entender mejor los mecanismos asociados al dolor y a mejorar el tratamiento del dolor de espalda, a través de alternativas como la Quiropráctica.

Un grupo de investigadores del *Madrid College of Chiropractic* del Real Centro Universitario Escorial-Mª Cristina, la Fundación Jiménez-Díaz, la Universidad de Alcalá de Henares y la universidad de Quebec en Trois-Rivières (Canadá), está desarrollando un Trabajo de Investigación para cuyo desarrollo necesitan la participación de voluntarios con dolor lumbar crónico. Este trabajo formará parte de la tesis de doctorado de Carlos Gevers Montoro, que está cursando este programa en la Universidad de Montréal, también en Canadá. El presente documento contiene la información necesaria para que usted decida si quiere participar o no en este estudio.

PROCEDIMIENTO:

El objetivo de este estudio es el de investigar los efectos que tiene la manipulación quiropráctica sobre el dolor lumbar crónico. Para ello, mediremos una serie de variables clínicas relacionadas con su dolor, las características del mismo, su umbral y sensibilidad ante el dolor, y la presencia de unas moléculas relacionadas con la inflamación en su orina. Para el estudio hemos establecido 2 grupos, a los que serán asignados los participantes de manera aleatoria antes del inicio del estudio, con el objetivo de determinar si existen diferencias entre ellos. A un grupo se le aplicará una sesión de manipulación quiropráctica en la región lumbar, y al otro, una sesión de manipulación *placebo*. Ambos procedimientos son indistinguibles el uno del otro y se utilizan frecuentemente en la práctica clínica y en protocolos de investigación del mundo entero. Para este proyecto, necesitamos la participación de 100 adultos voluntarios, entre los 18 y 70 años.

Una vez determinado si usted puede participar en el estudio mediante el cuestionario de selección, se le citará para acudir a consulta con una muestra de orina tomada en ayunas, a la que se asignará un código numérico, y se le realizará una exploración física que confirmará que puede participar en el estudio. En caso afirmativo, se le solicitará que rellene tres cuestionarios relacionados con el dolor y se procederá a medir su umbral de dolor en varias regiones del cuerpo. Ese mismo día, se iniciará la primera sesión de tratamiento basado en dos manipulaciones en la columna vertebral. Ambas son inocuas y no presentan riesgos para su salud. Esta primera sesión durará unos 60-90 minutos.

Después de esta sesión, se planificarán las siguientes 11 sesiones, con una frecuencia de 3 sesiones por semana (total de 4 semanas). En las siguientes sesiones, se le realizarán una serie de preguntas cortas que responderá en el ordenador antes de realizar las manipulaciones. Todas las sesiones se desarrollarán de esta manera y tendrán una duración de unos 15-20 minutos, excepto la última sesión (número 12), en la cuál se le solicitará que acuda con una segunda muestra de orina, se volverán a medir los umbrales de dolor y se repetirán los cuestionarios completados en la primera sesión. Esta sesión durará cerca de los 60 minutos. Un mes después de la conclusión del estudio, nos pondremos en contacto con Ud. para hacerle una serie de preguntas cortas sobre su estado clínico. Para la organización de las sesiones, el coordinador del estudio estará en contacto con Ud. vía WhatsApp o e-mail, según su preferencia.

Sus únicas obligaciones son las de cumplir con las visitas y actividades del estudio, y notificar cualquier evento adverso que pueda experimentar en relación con el mismo. La participación no supondrá ningún coste para Ud., sino al revés, podría beneficiarle para su dolor. Las técnicas de manipulación que se emplearán en el estudio están recomendadas por guías de práctica clínica para el tratamiento del dolor lumbar. Los riesgos más habituales asociados a estas técnicas son la rigidez muscular, el aumento del dolor lumbar o molestias que irradian por la pierna, todas de carácter pasajero. El investigador encargado de realizar el tratamiento dispone de una póliza de seguros que se ajusta a la legislación vigente (Real decreto 1090/2015) y que le proporcionará la compensación e indemnización en caso de menoscabo de su salud o de lesiones que pudieran producirse en relación con su participación en el estudio, siempre que no sean consecuencia de la propia enfermedad que se estudia o de la evolución propia de su enfermedad como consecuencia de la ineficacia del tratamiento.

En caso de haber recibido la manipulación *placebo*, se le propondrá a continuación un tratamiento *real* de 4 semanas de duración (un total de 12 sesiones) sin ningún coste para Ud. En caso de haber recibido el tratamiento *real* durante el estudio, Ud. podrá decidir si continuar con el tratamiento quiropráctico una vez finalizado el estudio, asumiendo Ud. los cargos habituales.

Para evaluar los datos recogidos y tener en cuenta los factores que puedan influir en éstos, necesitaremos también recoger datos personales, como su edad o nivel de estudios además de tres cuestionarios, por lo que para participar en el estudio también tendrá que autorizarnos para poder consultar el historial clínico recogido en el Centro Quiropráctico, si fuera necesario además de permitirnos utilizar los datos recogidos en los cuestionarios, de forma totalmente anónima.

CONFIDENCIALIDAD:

En todo momento sus datos serán tratados con absoluta confidencialidad. Nadie ajeno al estudio tendrá acceso a los datos que recojamos, y esos datos nunca serán públicos de manera individual (es decir, nadie ajeno al estudio podrá saber qué datos corresponden específicamente a usted). Además, estos datos tampoco podrán ser usados para ningún fin distinto a los objetivos que este estudio persigue. Sus datos personales solo serán conservados en la base de datos del Centro Quiropráctico,

cuyo acceso está protegido bajo contraseña y restringido a las personas involucradas en su atención clínica. Los datos correspondientes al estudio estarán asociados a un código numérico que impedirá su identificación. Estos datos serán almacenados en formato físico y digital, en un archivador bajo llave y en un disco duro protegido mediante contraseña durante 25 años desde la conclusión del estudio. Solamente el investigador principal tendrá acceso a la totalidad de los datos. Las muestras de orina recogidas serán identificadas con el código del estudio y conservadas temporalmente en un frigorífico a -20ºC en el Centro Quiropráctico, para ser trasladadas posteriormente a la Universidad de Alcalá de Henares, lugar en el que serán analizadas y conservadas hasta la conclusión del estudio.

De acuerdo con el Reglamento General de Protección de Datos (Reglamento EU 2016/679), además de los derechos de acceso, rectificación, oposición y cancelación de datos, también tiene derecho a limitar el tratamiento de datos y solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar sus derechos, diríjase al investigador principal del estudio o al delegado de protección de datos (secretaria@rcumariacristina.com). Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho/a.

¿Para qué se utilizarán mis datos?
Sus datos son necesarios para mejorar el tratamiento no farmacológico del dolor lumbar, y en particular para el desarrollo y la introducción en el mercado de manera segura del tratamiento quiropráctico. Por lo tanto, se utilizarán según lo planeado en este estudio, así como dentro de las actividades de investigación relacionadas necesarias para estos objetivos con el fin de:

- comprender cómo funciona el tratamiento de manipulación vertebral y actuaciones similares,
- comprender mejor la lumbalgia crónica y los problemas de salud asociados,
- desarrollar pruebas de diagnóstico para la lumbalgia crónica
- aprender de estudios anteriores para planificar nuevos estudios,
- publicar los resultados de la investigación en revistas científicas o utilizarlos con fines educativos.

¿Cómo se comunicarán los resultados?
El promotor publicará el protocolo y los resultados del estudio a través del Registro Estadounidense www.clinicaltrials.gov. El promotor está obligado a publicar los resultados, tanto positivos como negativos, de los ensayos clínicos autorizados, preferentemente, en revistas científicas antes de ser divulgados al público no sanitario, con independencia de las obligaciones de publicación del informe de los resultados en el registro y de lo establecido al respecto en el Reglamento (UE) n.º 536/2014 del Parlamento Europeo y del Consejo, de 16 de abril de 2014.

PREGUNTAS: Si usted tiene preguntas acerca del procedimiento puede consultar en cualquier momento del estudio, antes, durante y después de su participación en el mismo, tanto con la persona que le ha entregado esta hoja informativa o dirigirse al responsable de su coordinación: Carlos Gevers Montoro (correo electrónico: cgevers@rcumariacristina.com ; teléfono de contacto: 644 439 221).

Habiendo leído el documento informativo y estando de acuerdo con los aspectos tratados en el mismo acepto participar en el Trabajo de Investigación "Eficacia de la terapia manipulativa quiropráctica en pacientes con lumbalgia crónica primaria: un estudio preliminar" y contribuir al desarrollo del mismo.

Firma del participante_____ Fecha_____

INVESTIGADOR PRINCIPAL: Dra. Arantxa Ortega de Mues aortega@rcumariacristina.com

REAL CENTRO UNIVERSITARIO
Escorial – María Cristina

CONSENTIMIENTO INFORMADO

NOMBRE Y APELLIDOS: _____

Código: _____ (no rellenar esta casilla)

"Eficacia de la terapia manipulativa quiropráctica en pacientes con lumbalgia crónica primaria: un estudio preliminar"

D/Dña. (nombre y apellidos)_____

Habiendo leído la hoja de información acerca del estudio,
Habiendo sido informado suficientemente de en qué va a consistir,
Habiendo preguntado y solucionado cuantas dudas tenía al respecto,

Participo voluntariamente en el mismo siempre y cuando:

1. Mis datos sean tratados de forma confidencial y solamente por parte de los profesionales que forman parte de la investigación.
2. Pueda retirarme del estudio en el momento en que así lo desee, sin dar explicaciones y sin que esto afecte a mi tratamiento ni a la atención sanitaria que reciba.
3. Pueda preguntar en cualquier momento cualquier duda acerca del desarrollo del estudio.

Cumpliéndose lo anteriormente dicho, participo libremente en el desarrollo de dicho estudio científico y acepto que mis datos sean usados en él.

Firma participante:_____ Fecha: _____

Firma investigador:_____ Fecha: _____

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 19-20
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	4,5
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12,13,15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13,14, Figs 1,2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8,12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16-17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17-18

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Included in consent form
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16-17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13-14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17-18
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	In consent form

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Mechanisms of Chiropractic Spinal Manipulative Therapy for Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial

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Secondary Subject Heading:	Immunology (including allergy), Rehabilitation medicine
Keywords:	Clinical trials < THERAPEUTICS, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, COMPLEMENTARY MEDICINE, IMMUNOLOGY

Mechanisms of Chiropractic Spinal Manipulative Therapy for Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial

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Abstract

Introduction

Chronic low back pain (CLBP) is a highly prevalent and disabling condition. Identifying subgroups of patients afflicted with CLBP is a current research priority, for which a classification system based on pain mechanisms was proposed. Spinal manipulative therapy (SMT) is recommended for the management of CLBP. Yet, little data are available regarding its mechanisms of action, making it difficult to match this intervention to the patients who may benefit the most. It was suggested that SMT may influence mechanisms associated to central sensitisation. Therefore, classifying CLBP patients according to central sensitisation mechanisms may help predict their response to SMT.

Methods and analysis

This protocol describes a randomised placebo-controlled trial aiming to examine which variables linked to central sensitisation may help predict the clinical response to SMT in a cohort of CLBP patients. One hundred patients with chronic primary low back pain will be randomized to receive 12 sessions of SMT or placebo SMT over a 4-week period. Pain intensity and disability will be assessed as primary outcomes after completing the 4-week treatment (primary endpoint), and at 4- and 12-week follow-ups. Baseline values of two pain questionnaires, lumbar pressure pain thresholds, concentrations of an inflammatory cytokine and expectations of pain relief will be entered as predictors of the response to SMT in a multiple regression model. Changes in these variables after treatment will be used in a second multiple regression model. The reference values of these predictors will be measured from 50 age and sex-matched healthy controls to allow interpretation of values in patients. Mixed analyses of variance will also be conducted to compare the

primary outcomes and the predictors between groups (SMT vs. placebo) over time (baseline vs. post-treatment).

Ethics and dissemination: Ethical approval was granted by the Fundación Jiménez Díaz Clinical Research Ethics Committee.

Trial registration number: NCT05162924

Keywords: Randomized controlled trial; Low back pain; Patient stratification; Central Sensitization; Chiropractic Manipulation

Strengths and limitations of this study:

- This study will expand our understanding of the relevance of clinical, psychological, psychophysical and inflammatory variables in predicting the response of patients with chronic low back pain to manual therapy.
- The design including a control group with healthy participants will allow confirming the usefulness of a classification system for patients with chronic primary low back pain according to the underlying pain mechanisms.
- The blinding of outcome assessors, statistician, laboratory technician, and of the investigator providing care to the patients' progress will contribute to reduce bias.
- A high degree of similarity between the sham and real manipulations increases the odds of successfully blinding participants. However, the sham intervention may produce clinical effects.
- Clinical trials on manual therapy, including the present study, are limited by the impossibility of blinding the investigator providing care to the intervention.

Introduction

Low back pain (LBP) is the single most important cause of disability globally,[1] with a high proportion of patients whose pain persists or recurs.[1-4] Aiming to identify patient profiles that respond more favourably to specific treatments and their prognosis, recent investigations highlight the importance of identifying subgroups among people with chronic LBP (CLBP). One of the proposed classification systems stratifies patients into specific subgroups according to pain mechanisms (nociceptive, neuropathic or central sensitisation).[5-10] It has been suggested that a large proportion of CLBP patients presents chronic primary pain, which has been linked to altered nociceptive processing.[11 12] Among the phenomena that may underlie this aberrant processing, central sensitization (CS) is likely the predominant mechanism,[12 13] and its involvement in CLBP deserves further research.[14]

One of the currently recommended interventions for the management of CLBP is spinal manipulative therapy (SMT).[15 16] However, not all patients have an identical response.[17] There is insufficient data to determine which CLBP subgroups respond better to this intervention.[18 19] This may be so because the analgesic mechanisms are still largely unknown. It was proposed that the pain relieving effects of SMT partly rely on segmental pain inhibition processes.[20] These processes influence temporal summation of pain,[21 22] primary, and secondary hyperalgesia,[23 24] which may be measured to identify patients with a CS phenotype. Further, emerging data from animal and human studies support the hypothesis that SMT modulates the inflammatory response, influencing inflammatory cytokines.[25-28] Cytokines can induce neuroinflammation, which may mediate the development of CS[29 30] in the transition towards chronic pain.[8 31] SMT may thus relieve CLBP by impacting mechanisms linked to CS.[24 32-34]

Altered pain sensitivity in a specific musculoskeletal region may indicate nociplastic pain,[12 35 36] likely reflecting CS.[13] Abundant studies have reported that a subgroup of CLBP patients demonstrate segmental mechanical hyperalgesia, assessed via lower pressure pain thresholds (PPTs) in low back or lower extremity areas, when compared to healthy controls.[37-42] Changes in pain sensitivity are not confined to lumbar segments but rather may be present in remote anatomical locations.[14 38 43-45] Increased pain sensitivity is a clinical indicator possibly reflecting CS not just at the spinal level, but potentially implicating supraspinal structures.[8 14 31] Thus, it is plausible that mechanical pain sensitivity may play an important role in defining a CS phenotype in CLBP.[35]

Pain catastrophising has been described as a psychological trait and pain cognition linked to the development of CLBP with an altered pain sensitivity profile and a CS phenotype.[46-48] CLBP patients with higher pain sensitivity often demonstrate higher levels of catastrophising and other negative psychological traits[32 49-51] Similarly, higher pain catastrophising was associated with higher central sensitization inventory (CSI) scores.[52] The CSI and a clinical presentation suggestive of CS mechanisms has been proposed to identify a specific CLBP subgroup.[5 6 53 54]

Currently, the mechanisms leading to CS are still unknown, however, recent data suggest an important role for neuroinflammation.[29] Neuroinflammation may act at multiple levels, from the periphery[50] to the brain,[55] including the dorsal horn of the spinal cord.[56] The release of inflammatory cytokines, including the pro-inflammatory tumour necrosis factor alpha (TNF-α), was identified as a potential mechanism supporting this phenomenon.[29 30 57 58] Studies have shown an association between proinflammatory cytokines and CLBP,[59-62] suggesting that these may serve as a reliable biomarker to identify patients with a CS phenotype.

The classification of mechanism-based pain phenotypes is a complex and controversial task,[35 63 64] for which a variety of clinical, inflammatory, psychological, and psychophysical constructs must be considered.[9 65] Although CS may influence changes in pain sensitivity induced by SMT,[32] pain phenotyping has been scarcely applied to manual therapy research.[66] Therefore, the response of this subgroup of patients to SMT has yet to be assessed. The aim of this clinical trial is to investigate whether variables associated with a CS phenotype may help predict the response to SMT. The specific objectives are: 1) to identify the clinical, psychological, psychophysical and inflammatory variables linked to CS in a cohort of CLBP patients; and 2) to examine which of these variables predict the clinical response to SMT.

Methods

Experimental design and setting

The study consists of a mechanistic randomized placebo-controlled clinical trial with a mixed experimental design, whose objective is to assess which variables linked to CS in chronic pain patients can predict the response of CLBP patients to SMT (Figure 1). This protocol is reported according to the guidelines for clinical trial protocols Standard Protocol Items: Recommendations for Interventional Trials[67] (SPIRIT statement). Starting in November 2021, 150 participants will be recruited through the Madrid College of Chiropractic (MCC) teaching clinic in San Lorenzo de El Escorial (Spain). This includes 100 patients with CLBP and 50 healthy participants. The MCC clinic is a primary care setting specialized in spine care, including chiropractic and physical therapy services. Clinical, psychological, psychophysical and inflammatory variables will be measured in CLBP patients, which will be exposed to either SMT or a placebo SMT for 12 visits over a 4-week period. A group made up of 50 age and sex-matched healthy

volunteers will be used to determine the reference values of the same psychological, psychophysical, and inflammatory variables in a healthy population and compare them with the clinical population, before and after exposure.

Selection criteria

An investigator with over twenty years of clinical experience will be responsible for the selection of participants. To be eligible to participate in the study, patients must be 18 to 70 years old, receive a diagnosis of chronic primary LBP of at least 3-month duration, with or without leg pain (according to a clinical examination carried out at the MCC, see Figure 2A). If pain affecting the low back or lower limb is suspected to be predominantly of neuropathic origin, the patient will be excluded.[12] Additionally, patients will be excluded from the study if they present any of the following criteria: evidence of specific pathology as the cause of their CLBP, diagnosis of mental illness (with the exception of anxiety and depression, as these conditions are frequently comorbid with CLBP[68 69] and may suggest a CS phenotype[5 49]), presence of pain of equal or higher intensity affecting any other body region, use of corticosteroids, opiates or anti-cytokine medication, pregnancy, lumbar fusion surgery or recent laminectomy, having received chiropractic SMT in the 12 months prior to the beginning of the study.[5 50 51]

A cohort of healthy volunteers will be recruited to be used as a reference for the psychological, psychophysical, and inflammatory variables collected in the sample of CLBP patients. They will be age- and sex-matched to the patients allocated to the group receiving SMT. Individuals meeting the following criteria are eligible to participate: being 18 to 70 years old; presenting no current or chronic pain condition, as well as not having received any diagnosis of a systemic, inflammatory, neurological or psychiatric condition.

Randomisation, concealed allocation, and blinding

A computer application (random-number generator) will be used to generate a balanced randomisation sequence. Participants will be allocated in a 1:1 ratio to the intervention (SMT) or placebo arms following the chronological order of recruitment. Patients, outcome assessors and statistician will be blinded to group allocation. To confirm the efficacy of the patients' blinding, participants will respond in three occasions to the questions: "Do you think that the treatment you have received is a real chiropractic treatment for back pain?"; and "On a numerical rating scale of 0–100, please rate the degree of certainty for having received a real chiropractic treatment" (with 0 being total uncertainty and 100 being absolute certainty).[70]

Additionally, to avoid biases in the reporting of patient-reported outcome measures and to blind the investigator delivering the interventions, participants will provide these data via electronic questionnaires without the presence or interference of any investigator.

Interventions

Both real and placebo SMT will be delivered by a chiropractor with twenty years of experience that is part of the research team (CG-M). Two real SMT will be performed with the patient positioned in the lateral decubitus position (once on each side), by applying a high-velocity, low-amplitude force on the manipulated segment, with the aim of generating at least one joint cavitation (associated with an audible sound). For this, the chiropractor will use the hypothenar surface or the last phalanx of the 2nd and / or 3rd fingers of the hand to contact the spinous process of the vertebral segment with the most intense clinical pain (see supplemental Figure S1A), as detected in the initial patient

examination. In case of not perceiving a cavitation or satisfactory joint movement, SMT may be repeated once on each side. Therefore, all participants will receive a minimum of two and a maximum of four SMT thrusts. Participants in the placebo arm will receive a validated sham SMT that is very similar to SMT.[70] The patient is positioned in the same lateral decubitus position, with the lower leg in extension and the upper leg in flexion, and an unintended force is applied bilaterally to the gluteal region (Figure S1B). The number of real or placebo SMT attempts resulting in joint cavitation will be recorded. Participants in both groups will receive 3 treatment session per week for 4 weeks (see Figure 2). Healthy volunteers will receive no intervention during the same timeframe of 4 weeks (see Figure 3).

Outcome variables

Primary outcomes

Patients will rate their current CLBP intensity, as well as the average, minimum and maximum pain throughout the preceding seven days or since the time of the previous session, once the study is underway,[71 72] using a numerical rating scale between 0 (no pain) and 100 (maximum pain imaginable). Average pain intensity will be used as a primary outcome for all statistical analyses. The primary endpoint will be the change from baseline at the completion of the 12 sessions of SMT. For the follow-up, average pain intensity will be assessed 4 and 12 weeks after the completion of the trial.

Disability caused by CLBP will also be assessed as a primary outcome. After completing the case history, patients will fill out the Oswestry low back disability index questionnaire.[73] The questionnaire will also be completed after the 12th treatment session (primary endpoint), and at subsequent 4- and 12-week follow-ups.

Secondary outcomes

Five topics were identified to discriminate pain mechanisms between groups of patients, including CS mechanisms: clinical examination, questionnaires, quantitative sensory testing, laboratory tests, and imaging tests [9]. For the present study, all categories will be considered except the last one, which will only be used to rule out pain of suspected neuropathic or nociceptive aetiology. Variables belonging to these categories will be assessed for exploratory purposes and five of them will be examined as predictors of the response to SMT (two questionnaires, one quantitative sensory testing variable, one laboratory test variable and the expectations of pain relief).

Clinical examination variables

Data on the characteristics of the patients' CLBP will be collected at baseline for exploratory purposes: CLBP trajectory (duration and frequency) and localization. The duration of CLBP will be calculated as the number of months since the onset of the first episode of LBP. As for pain frequency, participants' CLBP trajectory will be classified as either fluctuating or episodic, depending on whether they recall asymptomatic periods of at least 4 weeks (episodic) or not (fluctuating).[74] For pain localization, patients will also draw the area affected by their pain on a tablet, using an application (Symptom Mapper) that will allow to calculate the degree of pain widespreadness.[75]

Additionally, CLBP will be classified as either proportionate or disproportionate to the degree or nature of the injury or pathology, with a discrete or diffuse distribution, according to criteria that were defined in the literature.[5 6] A diffuse rather than a discrete pain distribution was identified as a key criterion of a CS phenotype.[5 12] Also, classifying symptoms as proportionate (or not) was proposed to differentiate nociceptive pain from CS mechanisms.[35] The pattern of pain distribution and the provocation and response to aggravating and palliative factors will be assessed during case history and physical

examination. This will be complemented with information provided by diagnostic imaging when available.[9]

Finally, other variables will be reported such as the intake of pain medication compatible with the selection criteria, both at baseline and at after treatment. Similarly, whether the patient regularly smokes will be documented, since smoking has been associated with increased serum levels of pro-inflammatory cytokines.[76] The average number of hours of sleep will also be recorded, as it may help predict pain patterns.[77] Additionally, the presence of any chronic condition (including pain) that are comorbid with the CLBP will be recorded for exploratory purposes.

Questionnaire variables

The Pain Catastrophizing Scale (PCS) and CSI will be completed before the beginning of the treatment (baseline) and at a single follow-up after the 12th treatment session (see figures 2B and 2F).[78 79] The PCS will be used to identify specific pain cognitions that are frequently present in patients with a CS phenotype, this measure will be used to evaluate the association of CLBP with psychosocial factors described by Smart et al.[5] When combined with a clinical presentation suggestive of CS,[35] the CSI is an useful tool to identify patients compatible with certain CS mechanisms, particularly when using the cut-off value of 40 points.[80] Both these scores will be examined as predictors due to their intrinsic association with a CS phenotype.

In addition, the Beck Depression Inventory II (BDI-II) and the Generalized Anxiety Disorder scale (GAD) questionnaires will be used to screen and quantify symptoms of depression and anxiety.[81 82] The scores in these questionnaires will be measured both at baseline and after the 12th treatment session for exploratory purposes. We will examine whether these variables are associated with the primary outcomes. Pre

and post reference values of all questionnaires (PCS, CSI, BDI-II and GAD) will be taken from the healthy control participants in the same timeframe (Figure 3).

Quantitative sensory testing variables

Quantitative sensory testing based on the German protocol[83 84] will be performed with the aim of evaluating pain thresholds and sensitivity (see Figure 2C). Testing will consist of the exploration of the PPTs in deep tissues (Figure 4), using an algometer (Wagner Force Dial FPX, Greenwich, CT, USA). In addition, patients will rate the intensity of the first stimulus above threshold, using a numerical rating scale 0–100.[85] PPTs will be assessed by two interns completing their Master's in Chiropractic degree, after three months of training and pilot data collection. One of the two outcome assessors will be randomly assigned to each patient to perform both baseline and follow-up measurements. Two measurements will be taken bilaterally at a rate of about 50 kPa/s, and the arithmetic mean of both the thresholds and sensitivities reported calculated. Two consecutive measurements provide excellent reliability when assessing both populations with and without LBP,[86 87] while performing two repetitions per side of the lower back was proposed to optimize inter-session reliability.[88] PPTs will be performed over muscle tissue in 4 different locations. Primary pain will be assessed 2.5 cm lateral to the spinous process in the erector spinae[85] of the vertebral segment with the highest clinical pain intensity indicated by the patient and verified by palpation (Figure 4). Manual palpation will be performed to confirm that the selected segment either reproduces clinical pain or is the closest to the area (or to the centre) of CLBP symptoms. This will allow to assess the area of primary pain or hyperalgesia (segmental sensitivity). In addition, PPTs will be measured on both lower limbs in the dermatome corresponding to the segment of highest clinical pain intensity (dermatomal sensitivity), in the erector spinae four to six segments cranial to the most painful lumbar segment (heterosegmental sensitivity in a non-

symptomatic segment: secondary hyperalgesia), and in a remote location in both thenar eminences (widespread sensitivity). PPTs will be assessed during the initial examination for baseline and after the final treatment session (see Figures 2C and 2E). Reference values will be taken in healthy volunteers in the same locations as the CLBP participants receiving SMT (lumbar segmental, dermatomal, heterosegmental, widespread) at baseline and after 4 weeks (Figure 3).

Laboratory test variables: TNF-α as an inflammatory biomarker in urine

Before initiating the first treatment session and on the day of the last treatment session, urine samples will be collected (first morning micturition) and stored at -20º C (see Figure 2B and 2F). Additionally, the first morning micturition will be collected twice from healthy individuals in the same timeframe (two samples with a 4-week delay, see Figure 3).[62] Samples will be deidentified by using only the participant's ID code, and the laboratory technicians will be blinded to group allocation. Urine concentrations of tumour necrosis factor alpha (TNF-α) will be quantified for each sample using specific ELISA for TNF-α following manufacturer's instructions. The cytokine to creatinine ratio will be calculated to correct for differences in urine volumes.[89] TNF-α values, including urinary concentrations, were found to be elevated in CLBP patients and may respond to a treatment based on SMT.[25 27 59 62 90]

Expectations

Before initiating treatment, each participant will be asked to rate their expectations of pain relief upon completion of the study. To do this, a verbal evaluation will be provided using a visual analogue scale with the descriptors -100, equivalent to "total pain relief," 0, equivalent to "no change," up to +100, equivalent to "maximum pain increase". Such an assessment of patients' expectations allows to identify their contribution as part

of the placebo response, which were found to predict the response to treatment for chronic pain.[91]

Adverse events reporting

At the beginning of every SMT or placebo treatment sessions, patients will inform whether they have suffered any adverse effects that they feel could be related to the treatment received via an electronic questionnaire. Adverse effects will be classified into four categories most frequently reported after lumbar SMT as identified in a clinical trial: muscle stiffness, increased pain, radiating discomfort, and others.[92] In addition, patients will indicate whether they were triggered immediately, up to 24 hours, or more than 24 hours after the previous session, whether their duration was of minutes, hours (< 24 hours), between 24 and 48 hours, or longer than 48 hours,[92] and according to their intensity (very mild, mild, moderate, severe, very severe). The reporting of adverse events will be monitored by an investigator not involved in clinical care or examination. A 30-point increase in pain intensity or the reporting of moderate to severe adverse events in three consecutive visits will raise the alarm and the patient will be interviewed to determine whether care should be interrupted.

Healthy volunteers will be contacted one week prior to the follow-up appointment to rule out any of the following criteria that would exclude them from the follow-up: presence of pain or other symptoms for > 7 days, trauma or injury, initiating a new treatment or receiving a diagnosis compatible with the exclusion criteria. In addition, if the participant reports any pain or taking any pain medication within 24 hours of the follow-up, this session will be postponed for up to one week.

Procedures

Candidates interested in participating in the study will initially complete a form with the selection criteria (Supplemental Appendix 1). If the criteria are met, patients will schedule an appointment at the MCC clinic where they will read and sign a participant information sheet, and the informed consent (Supplemental Appendices 2 and 3). Subsequently, patients will undergo a clinical examination (consisting of a case history and physical examination) to confirm the diagnosis of chronic primary LBP, during which all outcomes will be collected, except for the urine sample that will be provided before the first treatment session. Patients will then participate in 12 treatment sessions divided into three weekly sessions for 4 weeks. All outcome measures will be re-assessed at the 12th and last treatment session (i.e., the primary endpoint). After completing data collection at the primary endpoint, patients allocated to the placebo arm will be offered the possibility of receiving the "real" SMT, free of charge, at the MCC. In addition, all patients will be contacted for the follow-up of CLBP intensity and disability, 4 and 12 weeks after the primary endpoint (Figure 2G). Meanwhile, healthy volunteers will participate in two visits (baseline and follow-up after 4 weeks) when all relevant outcomes will be assessed (Figure 3). The study will have a total estimated duration of one year.

Sample size calculation

To determine the ideal number of participants, the second aim to identify the variables linked to a CS phenotype that could help predict the response to treatment based on SMT for CLBP was considered. A multiple regression analysis will be performed using five independent variables described in the statistical analysis section as predictors. These variables include baseline values of local PPTs, urinary concentrations of TNF, scores in PCS and CSI questionnaires and a priori expectations of pain relief. For each

predictor variable, it is recommended to estimate about 10 sample elements, therefore we predict that a sample size of 50 patients per group will be necessary.[93] A total of 110 patients will be recruited, accounting for an estimated dropout rate of 5-10%.

Regarding the primary outcome variables, a reduction in pain intensity and disability after one month in patients who receive 12 sessions of SMT compared to placebo will be expected. We aim to detect small to moderate effects since it is a one-month intervention in patients with chronic pain unresolved by other treatments over at least 3 months. Therefore, based on an effect size of f = 0.175, an alpha of 0.05, a power of 0.8 for 2 groups and 2 repeated measures (baseline and primary endpoint), and a correlation between the repeated measures of 0.5, the size of the necessary sample is 34 patients per group, thus a total of 68 patients to detect statistically significant changes in clinical pain and disability. Therefore, the analysis based on the regression model to predict the clinical course provides with a large enough size for identifying small between-group differences.

Statistical analysis

The normal distribution of the data will be verified using the Kolmogorov-Smirnov test. Data deviating from normality will be transformed to obtain a normal distribution before being entered into the data analysis. In order to interpret the values in outcomes measured in patient groups, these will be compared with reference values obtained from the healthy controls to the CLBP group receiving SMT. This will allow characterizing the patients' groups (aim 1) to determine whether they show increased psychological symptoms, pain sensitivity and hyperalgesia as well as increased TNF-α levels compared with a reference healthy population. A series of mixed analyses of variance (ANOVA) will be performed to examine differences in PPTs, urinary TNF-α

levels, PCS, CSI, BDI-II and GAD scores before and after the 4-week treatment period between the three groups (control, SMT and placebo). To test a priori hypotheses, significant effects will be decomposed using planned comparisons. For the rest of the effects, Tukey's HSD will be used for testing any pairwise comparisons between group means.

Pearson's product-moment correlation analyses will be carried out to examine the association between the primary and secondary variables that demonstrate significant effects between groups over time. Subsequently, two multiple regression models will be used to examine the predictors of improvement in clinical pain and disability over time in patients who have received SMT (aim 2). The variables used as predictors for this analysis will be: baseline PCS and CSI score, baseline PPTs in the primary pain region, baseline TNF-α levels, and (baseline) expectations of pain relief. In addition, in another regression model, the changes (delta) in these variables (except expectations of pain relief, which are only measured a priori) after 4 weeks of treatment will be used as predictor variables. This is done to identify the variables most associated with clinical evolution to answer the mechanistic question.

The primary outcome variables (clinical pain intensity and disability) will be compared between groups (SMT vs. placebo) over time at the primary endpoint using mixed ANOVAs. Average pain intensity since the last treatment visit and in the seven days prior to the initial visit will be the pain variables used for statistical analyses. With an exploratory objective, the secondary variables (PCS, CSI, BDI-II, GAD scores, PPTs, degree of pain widespreadness, urinary cytokine levels, number and severity of reported adverse effects, presence of leg pain, pain medication use) will be compared between groups (SMT vs placebo) over time (baseline and post-treatment) using mixed ANOVAs. To test a priori hypotheses, significant effects will be decomposed using planned

comparisons. For the rest of the effects, Tukey's HSD will be used for testing any pairwise comparison between group means.

As recommended by White et al., efforts will be directed towards following up all participants for every time point.[94] An intention-to-treat analysis including all randomized study participants with a baseline endpoint assessment will be performed. The use of mixed model ANOVA allows to include all study participants with a lower attrition bias,[95] while handling missing data using maximum likelihood estimations. Further, a per-protocol analysis will be also performed excluding study participants who voluntarily drop out from the study, develop a severe adverse reaction (increase in >30 points average pain intensity associated to treatment) or fail to attend three consecutive visits, or more than two treatment weeks. Finally, in order to test whether the data is not missing at random, a sensitivity analysis will be conducted to explore the effect of attrition [94].

Data management and monitoring

All data will be collected at the MCC teaching clinic of the Real Centro Universitario María Cristina. The clinic utilizes a password-protected computer app that generates a patient file number linked to their clinical and personal data. This file number will be connected to a unique participant ID code made up of three numbers and a letter. This ID code will be used to deidentify all clinical trial data. Only the investigator involved in delivering care will have knowledge of which clinic file number corresponds to which study ID code. The participants' selection, information, consent forms and outcome measures collected in paper format will be securely stored in a file cabinet at the MCC clinic. Patient-reported outcome measures will be collected electronically using the study ID code to complete a google form (Google Inc.). Both paper and online data will

be transferred to a password-protected spreadsheet, only accessible to the principal investigator. Data will be stored deidentified for 25 years after final publication. The dataset will be made available after publication of the trial, upon request to the corresponding author.

Patient and public involvement

The local chiropractic patient and professional associations (Asociación Española de Usuarios de Quiropráctica and Asociación Española de Quiropráctica) have been involved throughout the study in the recruitment process and in promoting the trial. Upon completion of the study, the results will be disseminated to the patient community in the general assembly of the patient association, as per a formal agreement with the investigators.

Ethics and dissemination

This clinical trial obtained ethical approval by the Fundación Jiménez Díaz Clinical Research Ethics Committee. All participants in the study will sign an informed consent. Any amendment to the protocol will be communicated to the ethics review board and the clinical trial registry. The results of the study will be submitted for publication in peer-reviewed journals and disseminated via scientific conferences and presentations directed to the professional and patient associations.

Discussion

The stratification of patients with CLBP is essential to better understand the needs of individual patients and provide targeted treatment. A mechanism-based classification is a promising avenue to match patients with the care that is best suited with their CLBP

mechanism. However, there is an ongoing debate regarding the definition of these subgroups and the best available tools to diagnose them.[6 12 35 63 64] The most recent guidelines for the management of CLBP in both a primary care and a physiotherapy setting recommend SMT as one of the first options for care.[96 97] Nonetheless, it is not yet possible to identify which patients may benefit the most. The current study describes a protocol for a mechanistic randomised placebo-controlled trial that may contribute to unveil the CS-related mechanisms involved in CLBP relief by SMT. The main objective of the proposed trial is to provide some insight on potential mechanisms of SMT that may be particularly relevant for a subgroup of patients with CLBP. Grasping these mechanisms may help better guide conservative care for patients with CLBP by assessing clinical, neurophysiological, cognitive and/or biochemical variables at baseline.

Strengths and limitations

The main strength of the current study is the robust design using a validated placebo and assessing the blinding of participants, while ensuring the blinding of outcome assessors, statistician, laboratory technician. Moreover, the investigator delivering care will be blinded to the patients' progress. This will reduce biases that are typically introduced in manual therapy trials. Additionally, the use of a control group will help determine reference values and their stability in a healthy population, which has not been readily reported, particularly concerning urinary levels of inflammatory cytokines.[62] Further to this, the multidimensional approach to defining central sensitization and the mechanisms leading to it may render relevant data in better defining pain mechanisms involved in CLBP.

Regarding potential limitations, having only one clinician may limit the generalizability of the SMT effects. However, it also has the advantage of standardizing

the interventions and reducing variability in the procedures. It should also be noted that, although blinding the investigator providing care is desirable, it is impossible in manual therapy trials[98], including the present study. As the sham and real SMT have a high degree of similarity, effective blinding of participants is feasible.[70] The inability to distinguish the placebo from the real treatment is desirable to limit interpretation bias, particularly in a mechanistic trial as in the present study.[99] However, the sham SMT may rely on specific mechanisms that overlap with those of real SMT, leading to treatment effects.[99 100] Accordingly, the sham SMT should not be considered as an inert placebo and the lack of between-group differences should be interpreted with caution, with a potential risk for type II errors.

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Author contributions:

All authors contributed to the design of this protocol. CG-M and MP conceptualised and designed the protocol, except for every aspect related to laboratory analyses, which was conceptualised by AO-DM. The protocol was drafted by CG-M, and revised by MP and AO-DM. The statistical analysis was designed by MP. CG-M was responsible for ethical committee approval. All listed authors meet authorship criteria and have read and approved the final manuscript.

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Competing interests:

The authors have no conflict of interest and no commercial interest to declare.

Supplemental material:

The following documents are available as part of the supplemental material, in the Spanish language:

Supplemental figure S1: Photographs depicting the real (S1A) and sham (S1B) spinal manipulative therapy procedures.

Supplemental appendix 1: Participant selection form

Supplemental appendix 2: Participant information sheet

Supplemental appendix 3: Informed consent form

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Figure legends

Figure 1. CONSORT diagrams of the randomized clinical trial proposed, including the healthy participants' control arm.

Figure 2. Study protocol for the clinical trial. The recruitment process is illustrated in figure 2A, the collection of variable data during the initial examination is depicted with 2B and 2C (PPTs = Pressure Pain Thresholds). Figure 2D illustrates the treatment protocol (SMT = Spinal Manipulative Therapy) and Figures 2E and 2F the collection of variable data at the end of the 4-week treatment (i.e., primary endpoint), and Figure G the collection of pain intensity and disability data at the 4- and 12-week follow-ups.

Figure 3. Study protocol for the healthy control arm. The recruitment process is illustrated in 3A, the collection of variable data during the initial examination is depicted with 3B and 3C (PPTs = Pressure Pain Thresholds). Participants will receive no treatment (3D) and variable data will collected after four weeks for follow-up (3E and 3F).

Figure 4. Quantitative sensory testing. Measurement of pressure pain thresholds (PPTs) and suprathreshold sensitivity with the use of a Wagner Force Dial FPX algometer at different body locations. **(A)** Local segmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment with the highest intensity clinical pain identified by the patient or via posterior to anterior manual palpation. **(B)** Dermatomal segmental PPTs measured over muscle tissue located under the dermatome of the segment identified in (A). **(C)** Heterosegmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment located four segments cranial to the segment identified in (A). **(D)**

Remote segmental PPTs measured over muscle tissue in the centre of the thenar eminence. All participants whose image was used for this figure provided written consent to the inclusion of this image in the manuscript.

Supplemental figure S1: Photographs depicting the real (S1A) and sham (S1B) spinal manipulative therapy procedures. All participants whose image was used for this figure provided written consent to the inclusion of this image in the manuscript.

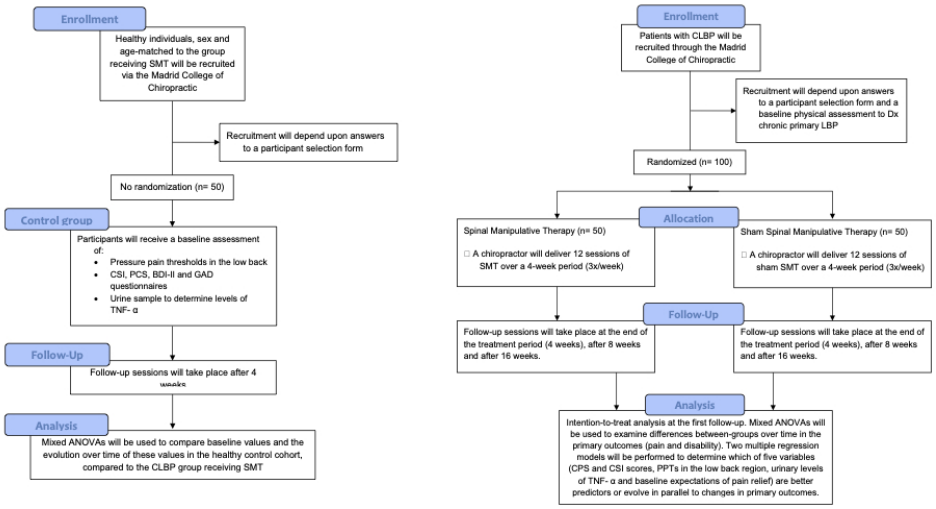

Figure 1. CONSORT diagrams of the randomized clinical trial proposed, including the healthy participants' control arm.

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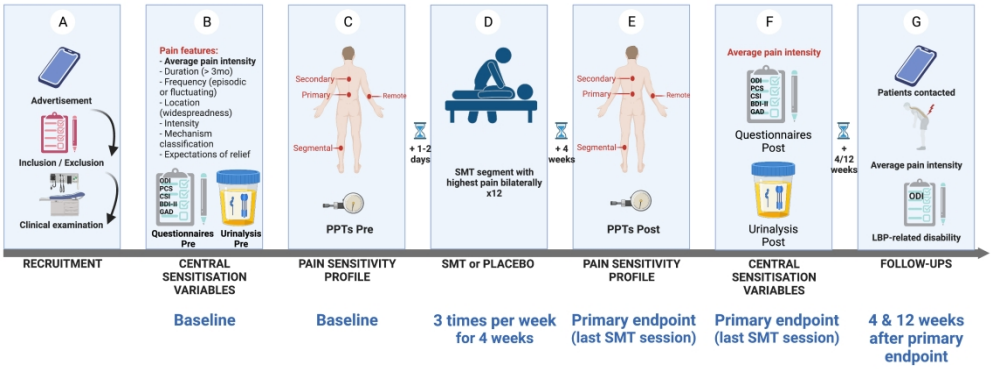

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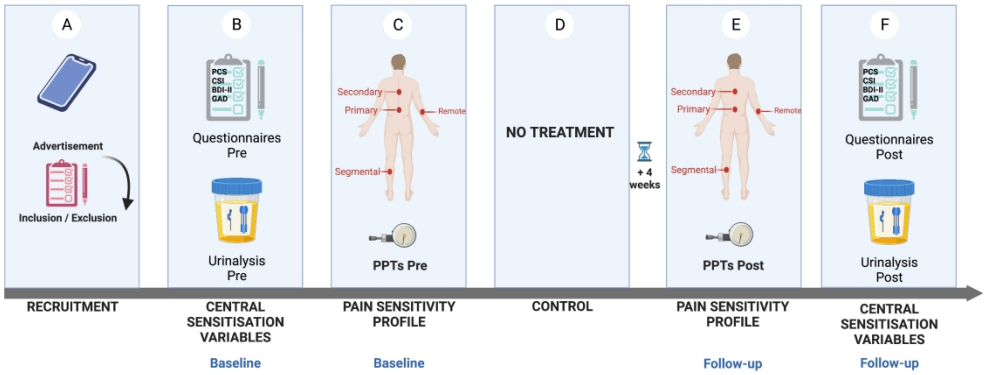


Study protocol for the healthy control arm. The recruitment process is illustrated in 3A, the collection of variable data during the initial examination is depicted with 3B and 3C (PPTs = Pressure Pain Thresholds). Participants will receive no treatment (3D) and variable data will collected after four weeks for follow-up (3E and 3F).

266x103mm (300 x 300 DPI)

Figure 4. Quantitative sensory testing. Measurement of pressure pain thresholds (PPTs) and suprathreshold sensitivity with the use of a Wagner Force Dial FPX algometer at different body locations. (A) Local segmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment with the highest intensity clinical pain identified by the patient or via posterior to anterior manual palpation. (B) Dermatomal segmental PPTs measured over muscle tissue located under the dermatome of the segment identified in (A). (C) Heterosegmental PPTs measured 2.5 cm lateral to the spinous process of the vertebral segment located four segments cranial to the segment identified in (A). (D) Remote segmental PPTs measured over muscle tissue in the centre of the thenar eminence.

250x190mm (146 x 146 DPI)

Supplemental figure S1: Photographs depicting the real (S1A) and sham (S1B) spinal manipulative therapy procedures.

528x351mm (72 x 72 DPI)

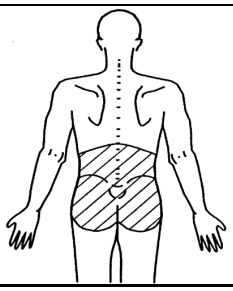
Hospital Universitario Fundación Jiménez Díaz Grupo quirónsalud
Universidad de Alcalá
UQTR Université du Québec à Trois-Rivières
MCC MADRID COLLEGE OF CHIROPRACTIC
REAL CENTRO UNIVERSITARIO Escorial – María Cristina

CUESTIONARIO PARA LA SELECCIÓN DE PARTICIPANTES

Nombre: Edad:

Número de teléfono:

Correo electrónico:

	Sí (especifique)	No
¿Padece Ud. de dolor lumbar en la zona indicada por el esquema, desde hace más de 3 meses? En caso afirmativo, ¿desde cuándo? 		
¿Sufre Ud. algún dolor de mayor intensidad o gravedad que el lumbar?		
¿Sufre Ud. dolor en sus manos/pulgares o en regiones cercanas a la lumbar?		
¿Ha sido Ud. diagnosticado con alguna enfermedad psiquiátrica o reumática?		
¿Toma Ud. algún medicamento regularmente para el dolor? ¿Cuál?		
¿Ha sido Ud. operado de la columna vertebral?		
¿Ha recibido Ud. tratamiento de manipulación vertebral en los últimos 12 meses?		
Si es Ud. mujer, ¿existe riesgo de estar embarazada?		

Firma del participante : _____ Fecha : _____

Firma del investigador : _____ Fecha : _____

REAL CENTRO UNIVERSITARIO
Escorial – María Cristina

DOCUMENTO INFORMATIVO RELATIVO AL DESARROLLO DEL PROYECTO DE INVESTIGACIÓN

TÍTULO DEL ESTUDIO	Eficacia de la terapia manipulativa quiropráctica en pacientes con lumbalgia crónica primaria: un estudio preliminar
CÓDIGO DEL ESTUDIO	EC113-21_FJD
PROMOTOR DEL ESTUDIO	Dr. Luis Álvarez Gálovich
INVESTIGADOR PRINCIPAL	Dra. Arantxa Ortega de Mues
CENTRO	Real Centro Universitario Escorial – María Cristina

INTRODUCCIÓN:

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por un Comité de Ética de la Investigación con medicamentos y por la Agencia Española de Medicamentos y Productos Sanitarios, de acuerdo a la legislación vigente, el Real Decreto 1090/2015 de 4 de diciembre y el Reglamento Europeo 536/2014 de 16 de abril, por los que se regulan los ensayos clínicos con medicamentos. Nuestra intención es que usted reciba la información correcta y suficiente para que pueda decidir si acepta o no participar en este estudio. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir. Además, puede consultar con las personas que considere oportuno.

Debe saber que su participación en este estudio es voluntaria y que puede decidir NO participar. Si decide participar, puede cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su atención sanitaria. No obstante, si participa en este estudio y nos permite evaluar su respuesta, nos estará ayudando a entender mejor los mecanismos asociados al dolor y a mejorar el tratamiento del dolor de espalda, a través de alternativas como la Quiropráctica.

Un grupo de investigadores del *Madrid College of Chiropractic* del Real Centro Universitario Escorial-Mª Cristina, la Fundación Jiménez-Díaz, la Universidad de Alcalá de Henares y la universidad de Quebec en Trois-Rivières (Canadá), está desarrollando un Trabajo de Investigación para cuyo desarrollo necesitan la participación de voluntarios con dolor lumbar crónico. Este trabajo formará parte de la tesis de doctorado de Carlos Gevers Montoro, que está cursando este programa en la Universidad de Montréal, también en Canadá. El presente documento contiene la información necesaria para que usted decida si quiere participar o no en este estudio.

PROCEDIMIENTO:

El objetivo de este estudio es el de investigar los efectos que tiene la manipulación quiropráctica sobre el dolor lumbar crónico. Para ello, mediremos una serie de variables clínicas relacionadas con su dolor, las características del mismo, su umbral y sensibilidad ante el dolor, y la presencia de unas moléculas relacionadas con la inflamación en su orina. Para el estudio hemos establecido 2 grupos, a los que serán asignados los participantes de manera aleatoria antes del inicio del estudio, con el objetivo de determinar si existen diferencias entre ellos. A un grupo se le aplicará una sesión de manipulación quiropráctica en la región lumbar, y al otro, una sesión de manipulación *placebo*. Ambos procedimientos son indistinguibles el uno del otro y se utilizan frecuentemente en la práctica clínica y en protocolos de investigación del mundo entero. Para este proyecto, necesitamos la participación de 100 adultos voluntarios, entre los 18 y 70 años.

Una vez determinado si usted puede participar en el estudio mediante el cuestionario de selección, se le citará para acudir a consulta con una muestra de orina tomada en ayunas, a la que se asignará un código numérico, y se le realizará una exploración física que confirmará que puede participar en el estudio. En caso afirmativo, se le solicitará que rellene tres cuestionarios relacionados con el dolor y se procederá a medir su umbral de dolor en varias regiones del cuerpo. Ese mismo día, se iniciará la primera sesión de tratamiento basado en dos manipulaciones en la columna vertebral. Ambas son inocuas y no presentan riesgos para su salud. Esta primera sesión durará unos 60-90 minutos.

Después de esta sesión, se planificarán las siguientes 11 sesiones, con una frecuencia de 3 sesiones por semana (total de 4 semanas). En las siguientes sesiones, se le realizarán una serie de preguntas cortas que responderá en el ordenador antes de realizar las manipulaciones. Todas las sesiones se desarrollarán de esta manera y tendrán una duración de unos 15-20 minutos, excepto la última sesión (número 12), en la cuál se le solicitará que acuda con una segunda muestra de orina, se volverán a medir los umbrales de dolor y se repetirán los cuestionarios completados en la primera sesión. Esta sesión durará cerca de los 60 minutos. Un mes después de la conclusión del estudio, nos pondremos en contacto con Ud. para hacerle una serie de preguntas cortas sobre su estado clínico. Para la organización de las sesiones, el coordinador del estudio estará en contacto con Ud. vía WhatsApp o e-mail, según su preferencia.

Sus únicas obligaciones son las de cumplir con las visitas y actividades del estudio, y notificar cualquier evento adverso que pueda experimentar en relación con el mismo. La participación no supondrá ningún coste para Ud., sino al revés, podría beneficiarle para su dolor. Las técnicas de manipulación que se emplearán en el estudio están recomendadas por guías de práctica clínica para el tratamiento del dolor lumbar. Los riesgos más habituales asociados a estas técnicas son la rigidez muscular, el aumento del dolor lumbar o molestias que irradian por la pierna, todas de carácter pasajero. El investigador encargado de realizar el tratamiento dispone de una póliza de seguros que se ajusta a la legislación vigente (Real decreto 1090/2015) y que le proporcionará la compensación e indemnización en caso de menoscabo de su salud o de lesiones que pudieran producirse en relación con su participación en el estudio, siempre que no sean consecuencia de la propia enfermedad que se estudia o de la evolución propia de su enfermedad como consecuencia de la ineficacia del tratamiento.

En caso de haber recibido la manipulación *placebo*, se le propondrá a continuación un tratamiento *real* de 4 semanas de duración (un total de 12 sesiones) sin ningún coste para Ud. En caso de haber recibido el tratamiento *real* durante el estudio, Ud. podrá decidir si continuar con el tratamiento quiropráctico una vez finalizado el estudio, asumiendo Ud. los cargos habituales.

Para evaluar los datos recogidos y tener en cuenta los factores que puedan influir en éstos, necesitaremos también recoger datos personales, como su edad o nivel de estudios además de tres cuestionarios, por lo que para participar en el estudio también tendrá que autorizarnos para poder consultar el historial clínico recogido en el Centro Quiropráctico, si fuera necesario además de permitirnos utilizar los datos recogidos en los cuestionarios, de forma totalmente anónima.

CONFIDENCIALIDAD:

En todo momento sus datos serán tratados con absoluta confidencialidad. Nadie ajeno al estudio tendrá acceso a los datos que recojamos, y esos datos nunca serán públicos de manera individual (es decir, nadie ajeno al estudio podrá saber qué datos corresponden específicamente a usted). Además, estos datos tampoco podrán ser usados para ningún fin distinto a los objetivos que este estudio persigue. Sus datos personales solo serán conservados en la base de datos del Centro Quiropráctico,

cuyo acceso está protegido bajo contraseña y restringido a las personas involucradas en su atención clínica. Los datos correspondientes al estudio estarán asociados a un código numérico que impedirá su identificación. Estos datos serán almacenados en formato físico y digital, en un archivador bajo llave y en un disco duro protegido mediante contraseña durante 25 años desde la conclusión del estudio. Solamente el investigador principal tendrá acceso a la totalidad de los datos. Las muestras de orina recogidas serán identificadas con el código del estudio y conservadas temporalmente en un frigorífico a -20ºC en el Centro Quiropráctico, para ser trasladadas posteriormente a la Universidad de Alcalá de Henares, lugar en el que serán analizadas y conservadas hasta la conclusión del estudio.

De acuerdo con el Reglamento General de Protección de Datos (Reglamento EU 2016/679), además de los derechos de acceso, rectificación, oposición y cancelación de datos, también tiene derecho a limitar el tratamiento de datos y solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar sus derechos, diríjase al investigador principal del estudio o al delegado de protección de datos (secretaria@rcumariacristina.com). Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho/a.

¿Para qué se utilizarán mis datos?
Sus datos son necesarios para mejorar el tratamiento no farmacológico del dolor lumbar, y en particular para el desarrollo y la introducción en el mercado de manera segura del tratamiento quiropráctico. Por lo tanto, se utilizarán según lo planeado en este estudio, así como dentro de las actividades de investigación relacionadas necesarias para estos objetivos con el fin de:

- comprender cómo funciona el tratamiento de manipulación vertebral y actuaciones similares,
- comprender mejor la lumbalgia crónica y los problemas de salud asociados,
- desarrollar pruebas de diagnóstico para la lumbalgia crónica
- aprender de estudios anteriores para planificar nuevos estudios,
- publicar los resultados de la investigación en revistas científicas o utilizarlos con fines educativos.

¿Cómo se comunicarán los resultados?
El promotor publicará el protocolo y los resultados del estudio a través del Registro Estadounidense www.clinicaltrials.gov. El promotor está obligado a publicar los resultados, tanto positivos como negativos, de los ensayos clínicos autorizados, preferentemente, en revistas científicas antes de ser divulgados al público no sanitario, con independencia de las obligaciones de publicación del informe de los resultados en el registro y de lo establecido al respecto en el Reglamento (UE) n.º 536/2014 del Parlamento Europeo y del Consejo, de 16 de abril de 2014.

PREGUNTAS: Si usted tiene preguntas acerca del procedimiento puede consultar en cualquier momento del estudio, antes, durante y después de su participación en el mismo, tanto con la persona que le ha entregado esta hoja informativa o dirigirse al responsable de su coordinación: Carlos Gevers Montoro (correo electrónico: cgevers@rcumariacristina.com ; teléfono de contacto: 644 439 221).

Habiendo leído el documento informativo y estando de acuerdo con los aspectos tratados en el mismo acepto participar en el Trabajo de Investigación "Eficacia de la terapia manipulativa quiropráctica en pacientes con lumbalgia crónica primaria: un estudio preliminar" y contribuir al desarrollo del mismo.

Firma del participante_____ Fecha_____

INVESTIGADOR PRINCIPAL: Dra. Arantxa Ortega de Mues aortega@rcumariacristina.com

REAL CENTRO UNIVERSITARIO
Escorial – María Cristina

CONSENTIMIENTO INFORMADO

NOMBRE Y APELLIDOS: _____

Código: _____ (no rellenar esta casilla)

"Eficacia de la terapia manipulativa quiropráctica en pacientes con lumbalgia crónica primaria: un estudio preliminar"

D/Dña. (nombre y apellidos)_____

Habiendo leído la hoja de información acerca del estudio,
Habiendo sido informado suficientemente de en qué va a consistir,
Habiendo preguntado y solucionado cuantas dudas tenía al respecto,

Participo voluntariamente en el mismo siempre y cuando:

1. Mis datos sean tratados de forma confidencial y solamente por parte de los profesionales que forman parte de la investigación.
2. Pueda retirarme del estudio en el momento en que así lo desee, sin dar explicaciones y sin que esto afecte a mi tratamiento ni a la atención sanitaria que reciba.
3. Pueda preguntar en cualquier momento cualquier duda acerca del desarrollo del estudio.

Cumpliéndose lo anteriormente dicho, participo libremente en el desarrollo de dicho estudio científico y acepto que mis datos sean usados en él.

Firma participante:_____ Fecha: _____

Firma investigador:_____ Fecha: _____

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 19-20
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
	6b	Explanation for choice of comparators	4,5
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12,13,15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13,14, Figs 1,2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8,12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16-17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17-18

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Included in consent form
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16-17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13-14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17-18
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	In consent form

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.