## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Mechanisms of Chiropractic Spinal Manipulative Therapy for Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial |
| **AUTHORS** | Gevers-Montoro, Carlos; Ortega-De Mues, Arantxa; Piché, Mathieu |

## VERSION 1 – REVIEW

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| **REVIEWER** | Glissmann Nim, Casper<br>University Hospital of Southern Denmark |
| **REVIEW RETURNED** | 03-Aug-2022 |

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| **GENERAL COMMENTS** | I reviewed the paper" Efficacy of Chiropractic Spinal Manipulative Therapy in Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial" with great interest. I enjoyed the read, and it is such an exciting design that potentially can provide some very needed answers. Also, the trial is registered correctly. However, I also have some considerations. Please notice that I have commented on the manuscript text first and then the abstract at the end. There are many comments, but I believe that with some adjustments, this could be a very well-read paper. Also, I find it essential for all professions involved in SMT. Limiting it to chiropractic is redundant and only reduces the interest from other groups. There are some more specific comments below. Again, thank you for conducting such interesting research. I am very much looking forward to the results.<br><br>Introduction:<br><br>I am having difficulty following the statement on p. 4, l. 15-20. I am not sure how subgrouping patients according to pain mechanisms is" One of the better studied classification systems," considering that nociplastic pain was adopted only a couple of years ago, with most of the references 5-10 being before this time. Also, recently some have criticized how clinically relevant it is, considering that we have no robust way of reliable assessing it (See more at PAIN: August 2022 - Volume 163 - Issue 8 - p e963 DOI: 10.1097/j.pain.0000000000002662). I agree with the authors that this is very interesting and a solid point to set the stage, but it does require less certainty, in my opinion. The following section is more appropriate and could stand by itself.<br><br>A quick notion about temporal summation, while it is of interest in the paper, examined temporal summation using cuff algometry (a relevant stimulus for MSK patients) on chronic LBP patients and found nothing, just a consideration whenever your result is available (https://chiromt.biomedcentral.com/articles/10.1186/s12998-021-00367-4) |

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| | Also, the same authors failed to find an association between CSI and QST results, and this is an uncommon finding (https://pubmed.ncbi.nlm.nih.gov/34668367/)<br><br>These are just considerations. There is definitely a link between altered pain sensitivity, inflammation, and psychology, but at this point, we must consider it speculative. It will be interesting to see your results also in a setting where manual therapy is applied to patients.<br><br>The aim is somewhat confusing, and I think it is due to the title. It states" efficacy," and then there is nothing about whether SMT is better than placebo for clinical efficacy, and this is obviously because you are looking at it mechanistically. I would change the title to" The mechanism of Spinal Manipulative Therapy in Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial." In this sense, I would also omit the" Chiropractor" part. There is nothing special about chiropractors performing SMT compared to other manual-therapy professions, and it would also allow your results to be more welcoming in other professional circuits. Then I would change the aim to three specific questions using a list format.<br>Objective 1: find a CS phenotype within persistent LBP<br>Objective 2: Which variables are associated with clinical response to SMT compared to a placebo<br>Objective 3: Prediction of clinical response using the variables<br><br>I can suggest reading this paper on association vs. prediction studies https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-020-01050-7. Especially Figure 1.<br><br>Method:<br><br>P6., L37, I would recommend writing" the protocol is reported according to SPIRIT."<br><br>I have no comments on the selection criteria or randomization as the study is already enrolling participants (according to the registration). The information is well presented.<br><br>Please add what side the patient will be lying on.<br><br>Please also state whether the clinician performing the SMT is part of the research team.<br><br>Usually, in RCTs, there is one primary outcome and one end-point. This sounds like pain at week 4 or perhaps 12? but please clarify. I would not call disability a primary outcome, as your sample size is based on pain. Instead, it is also a secondary outcome, just a clinical one, that should belong under" clinical examination variables" as part of the five topics.<br><br>CLBP trajectory (duration and frequency), how is this measured?<br><br>P. 10 at the top. Please elaborate on how clinicians will determine" whether the CLBP is proportionate or disproportionate to the degree or nature of the injury or pathology."<br><br>Please see my comment above about the use of CSI, especially using the cut-point of 40 in CLBP.<br><br>Generally, it is described that measurements are collected at baseline |

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| | and follow-up. Please clarify if this includes all follow-up time points, 4, 8, and 12 weeks.<br><br>P.12, l. 31: Perhaps I am misunderstanding but does reference 81 not suggest using the mean of 3 trials?<br><br>P. 12, L. 42, what is verified by palpation?<br><br>I am not familiar with the process of collecting TNF-α, so I cannot provide any revisions on this aspect.<br><br>Going through the method, I was a bit disappointed that temporal summation is not measured, considering its lengthy introduction. I would now suggest removing it altogether in the introduction to make it more relevant to the method actually used.<br><br>I enjoyed the section on adverse events; thank you for being so detailed about it.<br><br>Procedure:<br><br>Will participants in the placebo arm be offered" real" SMT after 12 weeks or after 4?<br><br>Also, would you mind providing some more information about MCC? It is comparable to a primary care setting or is a more typical chiropractic school clinic. In addition, the clinicians often referred to throughout the manuscript are these students or chiropractors, and how experienced are they? This is especially important as they are tasked heavily with some very detailed inclusion criteria and having to score patients for a predictor variable.<br><br>Could you please clarify your sample size calculation 1: You state five independent variables, but I can read multiple throughout the method section (The PPTs alone are 4, pain site, distant to pain site, leg, and hand). Do you apply some principal component analysis to cut it down to five variables, or do you select the most relevant variables from the five" topics"? If so, this ought to be stated here. Please clarify. Also, have you considered what to do about dropout or loss to follow-up?<br><br>For the RCT calculation, how come you did not consider the results from the Rubinstein review on chronic LBP? Here they state a change at one month as −7.55 (−19.86 to 4.76) on a 0 – 100 scale. Indicating no statistically significant difference. Perhaps your sham provides less mechanical input.<br><br>ANOVA should be defined in the text before first use<br><br>I would recommend highlighting the five key predictors referred to in the sample size calculation earlier to avoid confusion.<br><br>For the statistical analysis section, I would ensure that the proposed objectives (1 to 3) are reported in the same order to avoid confusion. Perhaps even with subheadings. In the objectives, nowhere does it say anything about the clinical efficacy of SMT compared to placebo, and that is not really what is interesting about this study either, but the mechanistic approach. Yet in the statistical analysis, I can primarily read about how the two groups are being compared.<br><br>I enjoyed the discussion and would recommend that the method reflects |

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| | more along this path rather than SMT vs. placebo. The major strength in this trial is the placebo group, not for clinical outcomes but the mechanistic ones.<br><br>P. 19, l 59:" and of the clinician delivering care to the patient's progress." It could be misleading. Please clarify<br><br>P. 19, l 60:" This will substantially reduce potential biases." Either it will substantially reduce biases, or it may reduce potential bias. Unfortunately, the clinician is still aware of the treatment, a bias that is impossible to overcome. Also, there is only one clinician, making the generalizability limited. This ought to be mentioned in the limitations.<br><br>p. 20: I am unsure how one would understand the following:" 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." Especially when you expect a significant enough effect, you only require 68 participants. I would recommend omitting this aspect and adding the other limitations mentioned.<br><br>In figure 2, I would rename the different parts as A, B, C, etc., to avoid confusion having a figure 1-5 in figure 2.<br><br>Abstract:<br><br>I would reflect on the objectives of the proposed introduction above. Making them more transparent and corresponding to those in the manuscript. If you have too many words, it would be easy to cut down on the initial part of the introduction.<br><br>Again in the method. I would state the design and the procedures and then describe the statistics, in short, reflecting the objectives.<br><br>In the" strength and limitation" under the keywords<br><br>I would remove the ones about bias and add something about the placebo group and the reference values from the healthy participants. These two aspects are new and by far the most interesting. |

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| **REVIEWER** | Ailliet, Luc<br>VU University Medical Centre Amsterdam |
| **REVIEW RETURNED** | 29-Aug-2022 |

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| **GENERAL COMMENTS** | The paper states inclusion of patients for this study was to start in November 2021. Is there / are there any specific reasons for this significant delay? |

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| **REVIEWER** | Bond, Bryan.<br>University of Saint Mary, Physical Therapy |
| **REVIEW RETURNED** | 04-Sep-2022 |

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| **GENERAL COMMENTS** | Thank-you the opportunity to review the manuscript titled, “Efficacy of Chiropractic Spinal Manipulative Therapy in Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial”. I appreciate the novel scientific premise associated with this manuscript. Overall, I appreciate the authors’ well-written manuscript and sound scientific design. However, please consider the following comments: |

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| | 1. I agree with the authors' statement that the primary limitation of the design lies with the sham or placebo manipulation. I also recognize the challenge of the application of an appropriate sham manipulation. Although the authors cite a valid placebo (Chaibi et al., 2015), it appears that the clinician will apply an external load/force to the participants as or stated in the manuscript "an unintended force is applied bilaterally to the gluteal region". It seems plausible that the "unintended force" applied relatively remote (i.e., gluteal region) to the most painful vertebral segment, may still elicit a neurophysiological response that influences nociception. For example, patients with elbow pain demonstrate PPT changes after cervical manipulation (Fernandez-Carnero, J., et al. (2008). "Immediate hypoalgesic and motor effects after a single cervical spine manipulation in subjects with lateral epicondylalgia." J Manipulative Physiol Ther 31(9): 675-681.), and patients with TMD pain demonstrate PPT changes after cervical mobilization (La Touche, R., et al. (2009). "The effects of manual therapy and exercise directed at the cervical spine on pain and pressure pain sensitivity in patients with myofascial temporomandibular disorders." J Oral Rehabil 36(9): 644-652.). Thus, the sham manipulation may have a "real" effect on the outcome measures. Please address this limitation within the manuscript. Also, it may be helpful for the readers to visualize the "real SMT" and "placebo SMT" (i.e., a figure or appendix/supplement with a video demonstration). Thanks.<br>2. From the manuscript, "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)." and "In case of not perceiving a cavitation or satisfactory joint movement, the SMT will be repeated once at the corresponding side." For clarification, each participant will receive a minimum of 2 thrusts (i.e., one left and one right), and possibly a maximum of 4 thrusts in the absence of cavitation? What if the manipulative attempts do not produce resultant cavitation? Please address these comments within the manuscript. Thanks.<br>3. What if some of the "healthy volunteers" develop pain during the 4-weeks from baseline to follow-up sessions? How will authors track these changes? How will authors account for this potential confounder? Please address these comments within the manuscript. Thanks. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Dr. Casper Glissmann Nim, University Hospital of Southern Denmark
Comments to the Author:
I reviewed the paper" Efficacy of Chiropractic Spinal Manipulative Therapy in Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial" with great interest. I enjoyed the read, and it is such an exciting design that potentially can provide some very needed answers. Also, the trial is registered correctly. However, I also have some considerations. Please notice that I have commented on the manuscript text first and then the abstract at the end. There are many comments, but I believe that with some adjustments, this could be a very well-read paper. Also, I find it essential for all professions involved in SMT. Limiting it to chiropractic is redundant and only reduces the interest from other groups. There are some more specific comments below. Again, thank you for conducting such interesting research. I am very much looking forward to the results.

Response: We thank the reviewer for very thoughtful comments and a thorough revision. We have responded to every comment and addressed all of them with significant changes to our manuscript. However, we have kept “Chiropractic” in the title, because it was requested by the ethics committee to emphasize what type of clinicians would be delivering the spinal manipulative therapy (SMT) both in the title and the manuscript.

Introduction:

I am having difficulty following the statement on p. 4, l. 15-20. I am not sure how subgrouping patients according to pain mechanisms is" One of the better studied classification systems," considering that nociplastic pain was adopted only a couple of years ago, with most of the references 5-10 being before this time. Also, recently some have criticized how clinically relevant it is, considering that we have no robust way of reliable assessing it (See more at PAIN: August 2022 - Volume 163 - Issue 8 - p e963 DOI: 10.1097/j.pain.0000000000002662). I agree with the authors that this is very interesting and a solid point to set the stage, but it does require less certainty, in my opinion. The following section is more appropriate and could stand by itself.

Response: We agree that this is just one of various proposed classification systems. We are also aware of the existing debate regarding the reliability of the diagnostic criteria for nociplastic pain, and how this term has become controversial. For this reason, we have reduced the certainty in our sentence and decided to use the more traditional concept (though also not completely accepted) of central sensitization, and now only mention nociplastic pain when introducing recent reviews specifically reviewing this concept and the link between both nociplastic pain and CS, and its diagnosis are discussed [1-3]. Changes can be read in pages 4-5:

One of the proposed classification systems stratifies patients into specific subgroups according to pain mechanisms (nociceptive, neuropathic or central sensitisation).[4-9] It has been suggested that a large proportion of CLBP patients presents chronic primary pain, which has been linked to altered nociceptive processing.[1 10] Among the phenomena that may underlie this aberrant processing, central sensitization (CS) is likely the predominant mechanism,[1 11] and its involvement in CLBP deserves further research.[12]

Thus, it is plausible that mechanical pain sensitivity may play an important role in defining a CS phenotype in CLBP.[2]

A quick notion about temporal summation, while it is of interest in the paper, examined temporal summation using cuff algometry (a relevant stimulus for MSK patients) on chronic LBP patients and found nothing, just a consideration whenever your result is available (https://chiromt.biomedcentral.com/articles/10.1186/s12998-021-00367-4)

Also, the same authors failed to find an association between CSI and QST results, and this is an uncommon finding (https://pubmed.ncbi.nlm.nih.gov/34668367/)

These are just considerations. There is definitely a link between altered pain sensitivity, inflammation, and psychology, but at this point, we must consider it speculative. It will be interesting to see your results also in a setting where manual therapy is applied to patients.

Response: We are aware of both articles. The findings from Holm et al. are relevant to our protocol. CSI and QST evaluate different constructs and we are examining which of these variables/constructs is more closely associated with the response to SMT. As discussed below, we have limited our emphasis on temporal summation, because we don’t measure temporal summation in the protocol. We agree that it should be mentioned for its relevance to CS mechanisms. We revised the introduction as follows:
- Page 4, second paragraph:
It was proposed that the pain relieving effects of SMT partly rely on segmental pain inhibition processes.[13] These processes influence temporal summation of pain,[14 15] primary, and secondary hyperalgesia,[16 17] which may be measured to identify patients with a CS phenotype.

- Page 6, first paragraph

The classification of mechanism-based pain phenotypes is a complex and controversial task,[2 18 19] for which a variety of clinical, inflammatory, psychological, and psychophysical constructs must be considered.[8 20] Although CS may influence changes in pain sensitivity induced by SMT,[21] pain phenotyping has been scarcely applied to manual therapy research.[22]

The aim is somewhat confusing, and I think it is due to the title. It states" efficacy," and then there is nothing about whether SMT is better than placebo for clinical efficacy, and this is obviously because you are looking at it mechanistically. I would change the title to" The mechanism of Spinal Manipulative Therapy in Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial." In this sense, I would also omit the" Chiropractor" part. There is nothing special about chiropractors performing SMT compared to other manual-therapy professions, and it would also allow your results to be more welcoming in other professional circuits. Then I would change the aim to three specific questions using a list format.
Objective 1: find a CS phenotype within persistent LBP
Objective 2: Which variables are associated with clinical response to SMT compared to a placebo
Objective 3: Prediction of clinical response using the variables

Response: We appreciate the reviewer's insight. We agree with the idea of generalizability but in this case specifically, as mentioned above, we must keep the word "Chiropractic" in the title as SMT was delivered by a chiropractor in a chiropractic setting and the Ethics Review Board had requested that this had to be very clearly stated; for Spanish regulations, SMT is not a regulated intervention. However, we revised the title as follows:

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

Regarding the objectives, we have only two, with an overarching aim. This was clarified as follows (page 6):

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.

I can suggest reading this paper on association vs. prediction studies https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-020-01050-7. Especially Figure 1.

Response: We understand that prediction requires a prospective experimental design, which is what we are using in this protocol. We also agree that a more robust predictive model needs to be tested by using clinical prediction rules first, and then confirmed in RCT's. We hope that our clinical trial results will be helpful in a design of clinical prediction rules for SMT in the future, including variables linked to pain mechanisms phenotypes.

Method:

P6., L37, I would recommend writing" the protocol is reported according to SPIRIT."

Response: The text was revised as follows on page 6:

This protocol is reported according to the guidelines for clinical trial protocols Standard Protocol Items: Recommendations for Interventional Trials[23] (SPIRIT statement).

I have no comments on the selection criteria or randomization as the study is already enrolling participants (according to the registration). The information is well presented.

Please add what side the patient will be lying on.

Response: Patients will receive two SM, one on each side. Therefore, we have revised the text accordingly to clarify (page 8, last paragraph):

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).

Please also state whether the clinician performing the SMT is part of the research team.

Response: The information was added on page 8:

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).

Usually, in RCTs, there is one primary outcome and one end-point. This sounds like pain at week 4 or perhaps 12? but please clarify. I would not call disability a primary outcome, as your sample size is based on pain. Instead, it is also a secondary outcome, just a clinical one, that should belong under" clinical examination variables" as part of the five topics.

Response: There are RCT's with multiple coprimary outcomes. One good example is a recent RCT by Goertz and colleagues, precisely on the use of chiropractic care for LBP [24]. Nonetheless, we also think that the reviewer makes an excellent point regarding disability, also because our RCT is mostly focused on pain-related mechanisms. For this reason, we have included only pain intensity as a primary outcome, and disability as a secondary outcome measure. In addition, we have clarified that our primary endpoint is at the end of the 12 sessions of SMT, and that there are two additional follow-ups 4 and 12 weeks after the end of treatment. Please refer to page 9, second paragraph for changes:

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.

Also, please not that throughout the text, the terminology has been standardized and adapted to these changes. We now use 'primary outcome' or 'primary variable' to refer exclusively to pain intensity, and 'primary endpoint' to refer to the change in baseline pain intensity at the completion of the 12 treatment sessions.

CLBP trajectory (duration and frequency), how is this measured?

Response: We thank the reviewer for pointing this out. Pain duration will be measured in months since the onset of the first LBP episode, while frequency of pain will be determined by using previously defined pain trajectories. Kongsted and colleagues found clear support to distinguish between two types of pain trajectories (episodic and fluctuating) that may be useful in the detection of CLBP subgroups.[25] This has been specified in the manuscript (page 10, second paragraph):

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).[25]

P. 10 at the top. Please elaborate on how clinicians will determine" whether the CLBP is proportionate or disproportionate to the degree or nature of the injury or pathology."

Response: We will be following the criteria originally proposed by Smart et al., where "disproportionate, non-mechanical unpredictable pattern of pain provocation in response to multiple/non-specific aggravating/easing factors'" were found to be the best predictors of CS pain.[4] These criteria were later reviewed and adopted by the guidelines published by Nijs and colleagues,[5] who recently reviewed and compared them to IASP criteria to diagnose nociplastic pain.[2] In line with

Shraim and colleagues' recent classification system, these criteria will be assessed by subjective pain ratings, and, when available, complemented with information from diagnostic imaging.[8] See the bottom of page 10 for changes:

A diffuse rather than a discrete pain distribution was identified as a key criterion of a CS phenotype.[1 4] Also, classifying symptoms as proportionate (or not) was proposed to differentiate nociceptive pain from CS mechanisms.[2] 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.[8]

Please see my comment above about the use of CSI, especially using the cut-point of 40 in CLBP.

Response: We understand the reviewer's concern regarding the cutoff score of 40 for the CSI. The CSI was not designed to be used single-handedly, but rather in combination with other diagnostic tools, including for CLBP [5 7]. We understand that the cutoff value may not parallel changes in pain sensitivity (or other constructs linked to CS). Instead, we consider the CSI to be one construct among others that may determine a (multifactorial) CS-phenotype. We revised the manuscript section describing this outcome measure (page 11, third paragraph):

When combined with a clinical presentation suggestive of CS,[2] the CSI is an useful tool to identify patients compatible with certain CS mechanisms, particularly when using the cut-off value of 40 points.[26]

Generally, it is described that measurements are collected at baseline and follow-up. Please clarify if this includes all follow-up time points, 4, 8, and 12 weeks.

Response: As mentioned above, this was clarified both in the manuscript and in Figure 2.

- Page 9:
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.

- Page 11:
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.[27] The questionnaire will also be completed after the 12th treatment session with the primary endpoint, and at subsequents 4- and 12-week follow-ups.

The Pain Catastrophizing Scale (PCS) and CSI[28 29] will be completed before the beginning of the treatment (baseline) and at a single follow-up after the 12th treatment session.

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.

- Pages 12
PPTs will be assessed during the initial examination for baseline, and after the final SMT session (see Figure 2E).

- Page 13:
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).

- Page 15:
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.

P.12, l. 31: Perhaps I am misunderstanding but does reference 81 not suggest using the mean of 3 trials?

Response: In another study, the mean of two or three trials was found to be equally reliable in asymptomatic participants. The same authors reported that one trial may be as reliable as two or three measurements in both asymptomatic and CLBP patients. Considering that we will test both population types, we decided to perform two trials. This is clarified in the revised manuscript (page 12):

Two consecutive measurements provide excellent reliability when assessing both populations with and without LBP,[30 31] while performing two repetitions per side of the lower back was proposed to optimize inter-session reliability.[32]

P. 12, L. 42, what is verified by palpation?

Response: Palpation will be used to verify that the segment indicated by the patient either reproduces clinical pain or is located as close as possible to the area of CLBP symptoms. We intend to select the segment most closely related to clinical pain rather than the segment where pain sensitivity is greater[17]. See page 12 for revisions.

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).

I am not familiar with the process of collecting TNF-α, so I cannot provide any revisions on this aspect.

Going through the method, I was a bit disappointed that temporal summation is not measured, considering its lengthy introduction. I would now suggest removing it altogether in the introduction to make it more relevant to the method actually used.

Response: It is essential to understand the potential implication of central sensitization mechanisms in studies that examine the mechanisms of SMT. Therefore, we reduced the emphasis on temporal summation, but we did not remove it completely. However, we agree to focus on hyperalgesia. The introduction now reads as follows (page 4, second paragraph):

It was proposed that the pain relieving effects of SMT partly rely on segmental pain inhibition processes[13]. These processes influence temporal summation of pain[14 15], primary, and secondary hyperalgesia,[16 17] which may be measured to identify patients with a CS phenotype.

I enjoyed the section on adverse events; thank you for being so detailed about it.

Procedure:

Will participants in the placebo arm be offered" real" SMT after 12 weeks or after 4?

Response: Yes, as mentioned above. This was clarified on page 15:

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).

Also, would you mind providing some more information about MCC? It is comparable to a primary care setting or is a more typical chiropractic school clinic.

Response: This is an important detail. We added the following to page 6:

The MCC clinic is a primary care setting specialized in spine care, including chiropractic and physical therapy services.

In addition, the clinicians often referred to throughout the manuscript are these students or chiropractors, and how experienced are they? This is especially important as they are tasked heavily with some very detailed inclusion criteria and having to score patients for a predictor variable.

Response: In order to avoid confusion, we avoided the use of the word clinician in the methods section. Instead, we used the term “investigator” and specified their task (i.e., delivering care), while the investigators assessing the patient are designated as “outcome assessors”. The outcome assessors are graduate students with training and expertise in the measurement of PPTs, as described on page 12:

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.

The inclusion of participants is the responsibility of the investigator delivering care, as specified on page 7:

An investigator with over twenty years of clinical experience will be responsible for the selection of participants.

Could you please clarify your sample size calculation 1: You state five independent variables, but I can read multiple throughout the method section (The PPTs alone are 4, pain site, distant to pain site, leg, and hand). Do you apply some principal component analysis to cut it down to five variables, or do you select the most relevant variables from the five" topics"? If so, this ought to be stated here. Please clarify. Also, have you considered what to do about dropout or loss to follow-up?

Response: We revised the statistical analysis section to clarify this issue and introduce the predictor variables early in the section on page 15. We also revised other manuscript sections, as discussed in one of the reviewer’s comments below.

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.

Response: Regarding dropout and loss to follow-up, we have provided this information on page 16:

A total of 110 patients will be recruited, accounting for an estimated dropout rate of 5-10%.

For the RCT calculation, how come you did not consider the results from the Rubinstein review on chronic LBP? Here they state a change at one month as −7.55 (−19.86 to 4.76) on a 0 – 100 scale. Indicating no statistically significant difference. Perhaps your sham provides less mechanical input.

Response: It is more conservative and careful to base our power calculation on the detection of a theoretical small effect in order to have sufficient statistical power to reach a conclusion with data from in this clinical trial. We are more confident that we will not miss an effect and report a false negative. The values in one study may be an indicator, but the effects vary from study to study.

ANOVA should be defined in the text before first use

Response: The acronym was defined on page 16, when it is now first introduced:

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 at baseline and primary endpoint between the three groups (control, SMT and placebo).

I would recommend highlighting the five key predictors referred to in the sample size calculation earlier to avoid confusion.

Response: We revised the text on page 10 to clarify, and page 15:

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).

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 the statistical analysis section, I would ensure that the proposed objectives (1 to 3) are reported in the same order to avoid confusion. Perhaps even with subheadings. In the objectives, nowhere does it say anything about the clinical efficacy of SMT compared to placebo, and that is not really what is interesting about this study either, but the mechanistic approach. Yet in the statistical analysis, I can primarily read about how the two groups are being compared.

Response: The text was revised to clarify (see pages 16-18).

I enjoyed the discussion and would recommend that the method reflects more along this path rather than SMT vs. placebo. The major strength in this trial is the placebo group, not for clinical outcomes but the mechanistic ones.

Response: The revisions made according to comments above strengthened the emphasis on the predictor variables, which is in line with this comment.

P. 19, l 59:" and of the clinician delivering care to the patient's progress." It could be misleading. Please clarify

Response: The text was revised to clarify on page 20, second paragraph:

Moreover, the investigator delivering care will be blinded to the patients' progress.

P. 19, l 60:" This will substantially reduce potential biases." Either it will substantially reduce biases, or it may reduce potential bias. Unfortunately, the clinician is still aware of the treatment, a bias that is impossible to overcome. Also, there is only one clinician, making the generalizability limited. This ought to be mentioned in the limitations.

Response: This was clarified on pages 20-21 as follows:

This will reduce biases that are typically introduced in manual therapy trials.
(…)
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[33], including the present study.

p. 20: I am unsure how one would understand the following:" 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." Especially when you expect a significant enough effect, you only require 68 participants. I would recommend omitting this aspect and adding the other limitations mentioned.

Response: The manuscript was revised including the limitations suggested by the reviewer, as detailed above. Also, we included all limitations in one paragraph (page 21):

It should also be noted that although blinding the investigator providing care is desirable, it is impossible in manual therapy trials[33], including the present study. As the sham and real SMT have a high degree of similarity, effective blinding of participants is feasible.[34] 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.[35] However, the sham SMT may rely on specific mechanisms that overlap with those of real SMT, leading to treatment effects.[35 36] 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.

In figure 2, I would rename the different parts as A, B, C, etc., to avoid confusion having a figure 1-5 in figure 2.

Response: During the revision process, Figure 2 was revised and we included a new Figure 3

See revised version of Figure 2, and new Figure 3

Abstract:

I would reflect on the objectives of the proposed introduction above. Making them more transparent and corresponding to those in the manuscript. If you have too many words, it would be easy to cut down on the initial part of the introduction.

Response: We agree with the reviewers that the objectives need to be presented according to the changes made in the manuscript. The abstract was revised as follows:

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.

Again in the method. I would state the design and the procedures and then describe the statistics, in short, reflecting the objectives.

Response: The abstract was revised as follows:

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).

In the" strength and limitation" under the keywords
I would remove the ones about bias and add something about the placebo group and the reference values from the healthy participants. These two aspects are new and by far the most interesting.

Response: we have also updated the strengths and limitations to reflect the suggestions made by the reviewer and the revised manuscript:

• 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.
Reviewer: 2
Dr. Luc Ailliet, VU University Medical Centre Amsterdam

Comments to the Author:
The paper states inclusion of patients for this study was to start in November 2021. Is there / are there any specific reasons for this significant delay?

Response: The delays at the beginning of the study are related to restrictions and other measures to mitigate the impact of the pandemic. Data collection was sometimes completely halted for over a month during because of surges in COVID-19 cases and hospitalizations. Data collection is currently ongoing and is planned to be completed in 2023.

Reviewer: 3
Dr. Bryan. Bond, University of Saint Mary, Allen College

Comments to the Author:
Thank-you the opportunity to review the manuscript titled, "Efficacy of Chiropractic Spinal Manipulative Therapy in Patients with Chronic Primary Low Back Pain: Protocol for a Mechanistic Randomised Placebo-Controlled Trial". I appreciate the novel scientific premise associated with this manuscript. Overall, I appreciate the authors' well-written manuscript and sound scientific design. However, please consider the following comments:

1. I agree with the authors' statement that the primary limitation of the design lies with the sham or placebo manipulation. I also recognize the challenge of the application of an appropriate sham manipulation. Although the authors cite a valid placebo (Chaibi et al., 2015), it appears that the clinician will apply an external load/force to the participants as or stated in the manuscript "an unintended force is applied bilaterally to the gluteal region". It seems plausible that the "unintended force" applied relatively remote (i.e., gluteal region) to the most painful vertebral segment, may still elicit a neurophysiological response that influences nociception. For example, patients with elbow pain demonstrate PPT changes after cervical manipulation (Fernandez-Carnero, J., et al. (2008). "Immediate hypoalgesic and motor effects after a single cervical spine manipulation in subjects with lateral epicondylalgia." J Manipulative Physiol Ther 31(9): 675-681.), and patients with TMD pain demonstrate PPT changes after cervical mobilization (La Touche, R., et al. (2009). "The effects of manual therapy and exercise directed at the cervical spine on pain and pressure pain sensitivity in patients with myofascial temporomandibular disorders." J Oral Rehabil 36(9): 644-652.). Thus, the sham manipulation may have a "real" effect on the outcome measures. Please address this limitation within the manuscript. Also, it may be helpful for the readers to visualize the "real SMT" and "placebo SMT" (i.e., a figure or appendix/supplement with a video demonstration). Thanks.

Response: We share the reviewer's interest in the placebo mechanisms of SMT (see section 2.4 in Gevers-Montoro et al, Eur J Pain, 2021[36]). The placebo SMT chosen for this study was reported to blind participants adequately[36]. However, as the reviewer suggests, this procedure may produce clinical effects. This is addressed in the limitation section of the revised manuscript (see the new paragraph in the limitations section, page 21). We have included a supplementary figure S1 were both the placebo and real SMT procedures are illustrated as per the reviewer's suggestion.

It should also be noted that although blinding the investigator providing care is desirable, it is impossible in manual therapy trials[33], including the present study. As the sham and real SMT have a high degree of similarity, effective blinding of participants is feasible.[34] 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.[35] However, the sham SMT may rely on specific mechanisms that overlap with those of real SMT, leading to treatment effects.[35 36] 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.

2. From the manuscript, “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).” and “In case of not perceiving a cavitation or satisfactory joint movement, the SMT will be repeated once at the corresponding side.” For clarification, each participant will receive a minimum of 2 thrusts (i.e., one left and one right), and possibly a maximum of 4 thrusts in the absence of cavitation? What if the manipulative attempts do not produce resultant cavitation? Please address these comments within the manuscript. Thanks.

Response: We thank the reviewer for this important comment. There will be a maximum of 2 attempts to obtain a cavitation on each side (total of 4) and the number of cavitations will be documented (0, 1 or 2) for SMT and placebo sessions. It is unclear whether joint cavitation has any influence in patient outcomes, which could explain clinical equivalence between manipulation and mobilization techniques[37]. However, on exploratory analyses, the number of cavitations will be used as a covariate to examine whether it has any impact on the outcomes. We clarified these issues on pages 8-9:

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 (see supplemental Figure S1A). 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.[34] 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.

3. What if some of the “healthy volunteers” develop pain during the 4-weeks from baseline to follow-up sessions? How will authors track these changes? How will authors account for this potential confounder? Please address these comments within the manuscript. Thanks.

Response: This is a very good point. Any healthy participant experiencing acute pain or other symptoms of > 7 days of duration, being injured, initiating any new treatment or receiving a diagnosis compatible with the exclusion criteria for this group will be excluded from the study. If the participant experiences pain or is taking pain medication < 24 hours prior to the follow-up session, this session will be postponed for a maximum of one week. Please see page 14:

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.

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## VERSION 2 – REVIEW

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| **REVIEWER** | Glissmann Nim, Casper<br>University Hospital of Southern Denmark |
| **REVIEW RETURNED** | 14-Nov-2022 |

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|---|---|
| **GENERAL COMMENTS** | I thank the authors for providing specific responses and adopting the manuscript accordingly. I have nothing further to add but to look forward to the results. |