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Osteopathy and physiotherapy compared to physiotherapy alone on fatigue in long COVID: Study protocol for a pragmatic randomized controlled superiority trial

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ABSTRACT

Objective: Fatigue is among the most common symptoms of the long-term effects of coronavirus (long COVID). This study aims to compare the effectiveness of osteopathic manipulative treatment (OMT) combined with physiotherapy treatment (PT) compared to PT alone on fatigue and functional limitations after two months post randomization in adults with long COVID.

Methods: This is a study protocol for a two-arm, assessor-blinded, pragmatic randomized controlled superiority trial. Seventy-six participants will be randomly allocated to OMT + PT or PT. The PT includes usual care interventions including motor and respiratory exercises targeting cardiorespiratory and skeletal muscle functions. The OMT entails direct and indirect musculoskeletal, visceral and cranial techniques. Patients will be evaluated before and after a 2-month intervention program, and at 3-month follow-up session. Primary objectives comprise fatigue and functional limitations at 2-month post randomization as assessed by the fatigue severity scale and the Post-COVID Functional State scale. Secondary objectives comprise fatigue and functional limitations at 3 months, and the perceived change post-treatment as assessed by the Perceived Change Scale (PCS-patient).

Registration: This protocol was registered (NCT05012826) and received ethical approval (38342520.7.0000.5235). Participant recruitment began in August 2021 and is expected to conclude in July 2023. Publication of the results is anticipated in 2023.

1. Background

The coronavirus disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—COVID-19—is causing a substantial increase in hospitalizations leading to overloads in global health systems [1,2]. Long-term effects of coronavirus—long COVID—comprise of the effects of COVID-19 that lasts for weeks or even months beyond the acute infection. Long COVID includes a wide spectrum of respiratory, neurologic, cardiovascular, gastrointestinal, and musculoskeletal symptoms, and an increased risk of death [1,3–5]. There are more than 50 known possible sequelae in long COVID, such as chronic fatigue, and the clinical manifestations may persist for weeks after the acute infection [6], leading to a decrease in quality of life [7]. This

condition reinforces the demand for healthcare and the need for a comprehensive approach for patients with long COVID.

Physiotherapy interventions may be required for patients with long COVID aiming to manage symptoms, prevent and restore the patients' functional status and enabling them to perform activities of daily living [3]. The physiotherapy approach for patients with long COVID includes motor and respiratory rehabilitation aiming at maintaining and/or improving joint mobility, muscle strength, and functional capacity [8]. A systematic review highlighted that to improve the rehabilitation in patients, especially in older adults with a severe respiratory illness on admission and after post ICU, some exercise regimens and habits can bring hope, confidence, and functional independence. The authors suggest this may be generalized to those treated for COVID-19, but

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maybe with personalized care. However, there is a lack of consensus on outcomes measures [9].

Osteopathy is a healthcare system that aims to promote the balance of physiological function, support homeostasis and encourage wellbeing [10–15]. In 1918, during the Spanish flu in the United States, osteopathy presented itself as one of the health resources made available to help fight the epidemic. In 2007, OMT once again presented itself as a possibility to help restore health to individuals affected by the H5N1 avian flu [16,17]. It is worth noticing though these studies are of the lowest evidence, often collections of research that is not directly relevant to the condition and with no indication of clinical relevance; also, most of them comprise hypothetical opinions on this matter. Studies on the OMT combined with standard medical care show that OMT can collaborate in the recovery of health in various clinical conditions [18–22], including shortening the length of stay and in-hospital mortality rates in the elderly with more severe pneumonia [23]. Altogether, the interest in the field but absence of reliable data justified an effort to assess the effects of OMT on fatigue in people with long COVID [16,24]. If found effective,

OMT may be recommended as an adjunct to other interventions for this population.

Fatigue is one of the most common and persistent sequelae in long COVID [6]. Fatigue is often a disabling symptom related to several clinical conditions related to systemic inflammatory processes. Pain and fatigue, for example, may overlap, suggesting that biological mechanisms, which include peripheral and central components, and identifiable neuronal networks, are present in both conditions [25]. In a systematic review of the effects of OMT on chronic inflammatory diseases, the data proved inconsistent but safe, suggesting more robust trials are warranted [26]. Hence, the primary aim of this trial is to test whether OMT combined with PT (OMT + PT) is superior to PT alone on fatigue and functional limitations two months post randomization in adults with long COVID. Secondly, this trial will investigate the effectiveness of OMT + PT and PT alone on fatigue, functional status, and perceived change post-treatment 3 months post-randomization in this population.

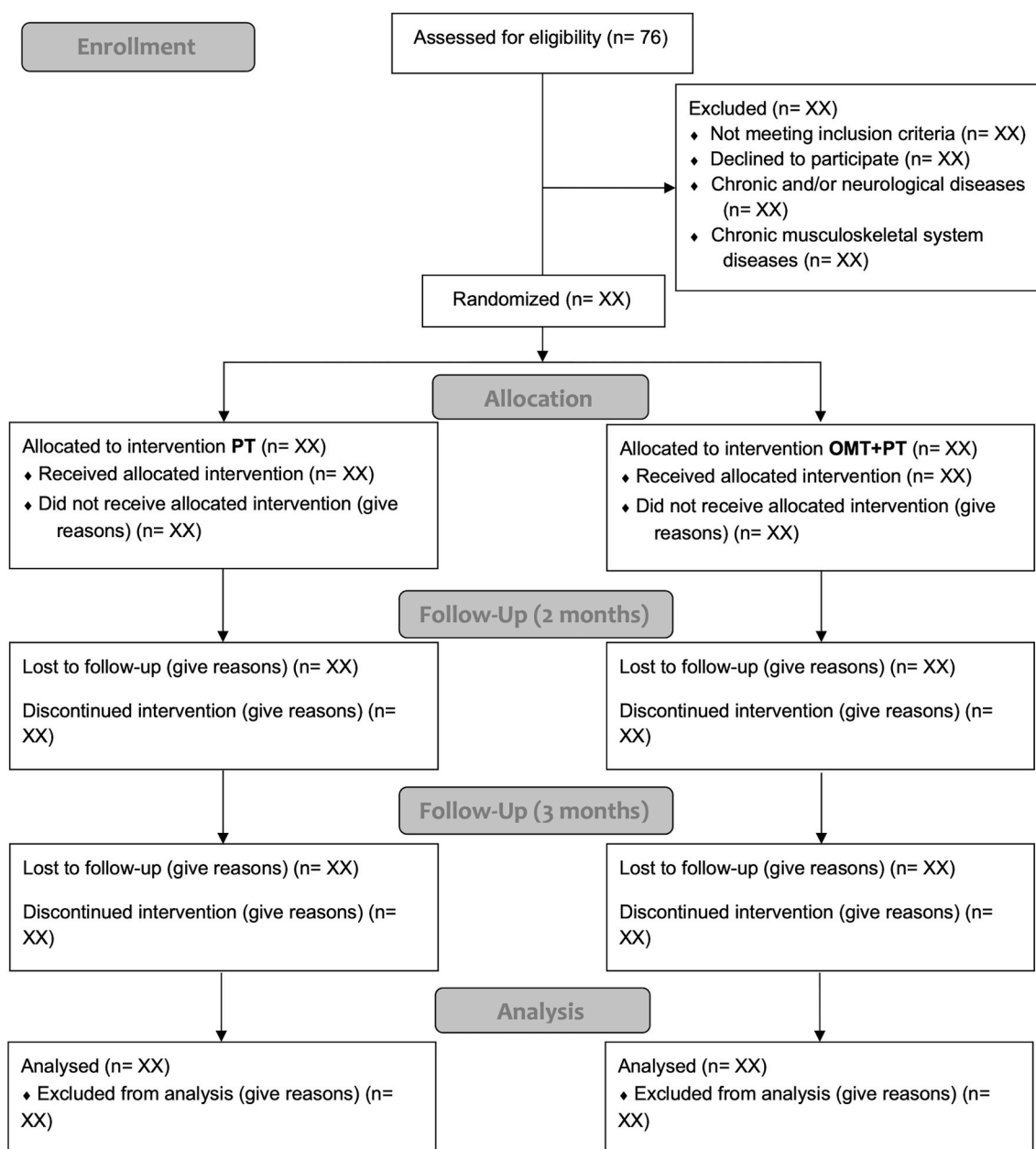


Fig. 1. Study flowchart.

2. Methods

2.1. Study design

This study is a two-arm, assessor-blinded, pragmatic randomized controlled superiority trial (Fig. 1). A pragmatic trial design was proposed based on the following [27]: both physiotherapy [28] and OMT [29] independently have promising evidence to be effective in the management of chronic fatigue; both physiotherapy and OMT are complex but feasible interventions as they are already included in the public health system as usual care, although only the former is delivered to all patients at our setting; and the urgent need to assess the efficacy of these interventions in real-world settings given the current morbidity of COVID-19 in Brazil to inform health policy-makers. The revised version of the PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2) [30] scores for this trial are: Elig. = 5; Recr.: 5; Setting = 5; Org. Int. = 5; Flex. Del. = 5; Flex. Adherence = 3; Follow-Up = 3; Prim. Out. = 5; Prim. An. = 5 (Fig. 2).

The trial will be conducted according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [31]. The trial results will be reported according to the CONSolidated Standards Of Reporting Trials (CONSORT) [32] (Supplementary File 1), the CONSORT extension for non-pharmacological trials [33], and the template for intervention description and replication (TIDieR) checklist [34]. This protocol was prospectively registered (ClinicalTrials.gov Identifier: NCT05012826).

2.2. Setting

This study will be conducted in a public health primary-to-tertiary setting, at Osteopathic Clinic outpatient at Engenho de Dentro Municipal Rehabilitation Center, Rio de Janeiro (Brazil).

2.3. Recruitment

Recruitment will be conducted in a public health primary-to-tertiary

setting at the Osteopathic Clinic outpatient at Engenho de Dentro Municipal Rehabilitation Center, Rio de Janeiro (Brazil). The referred patients will be carried out by physicians who had accompanied them during the infectious process of COVID-19, and because of long COVID, they recommend physiotherapy treatment. They can be allocated to the following rehabilitation sectors according to their necessities: Respiratory, Orthopedic, or Rheumatological. After contact being made with a potential participant, a researcher will evaluate whether the potential participant is eligible for the study. Potential participants will undergo a face-to-face assessment to provide additional information to confirm their eligibility before the baseline evaluation. The study researcher will discuss with the eligible participants the time demands of taking part in the study, and confirm that each participant can dedicate this time, to ease adherence to the interventions. During the baseline evaluation, one researcher will review the study protocol with the participants and collect written informed consent. Baseline outcome data will also be obtained during this session.

2.4. Participants

Participants will be screened for eligibility criteria. Inclusion criteria comprise age equal to or above 18 years; essential and clinical criteria for long COVID at baseline assessment (confirmed preceding infection with SARS-CoV-2, individuals referred for rehabilitation reporting fatigue as major symptom [35]; and ability to understand Portuguese well enough to be able to fill in the questionnaires. Exclusion criteria comprise conditions in which fatigue is also a major complain such as suspected or diagnosed chronic and/or neurological diseases (e.g., Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease); pre-existing, chronic diseases affecting the musculoskeletal system (e.g., fibromyalgia).

2.5. Randomization and allocation

A computer-generated sequence will be generated using a website (<http://www.jerrydallal.com/random/randomize.htm>) to allocate

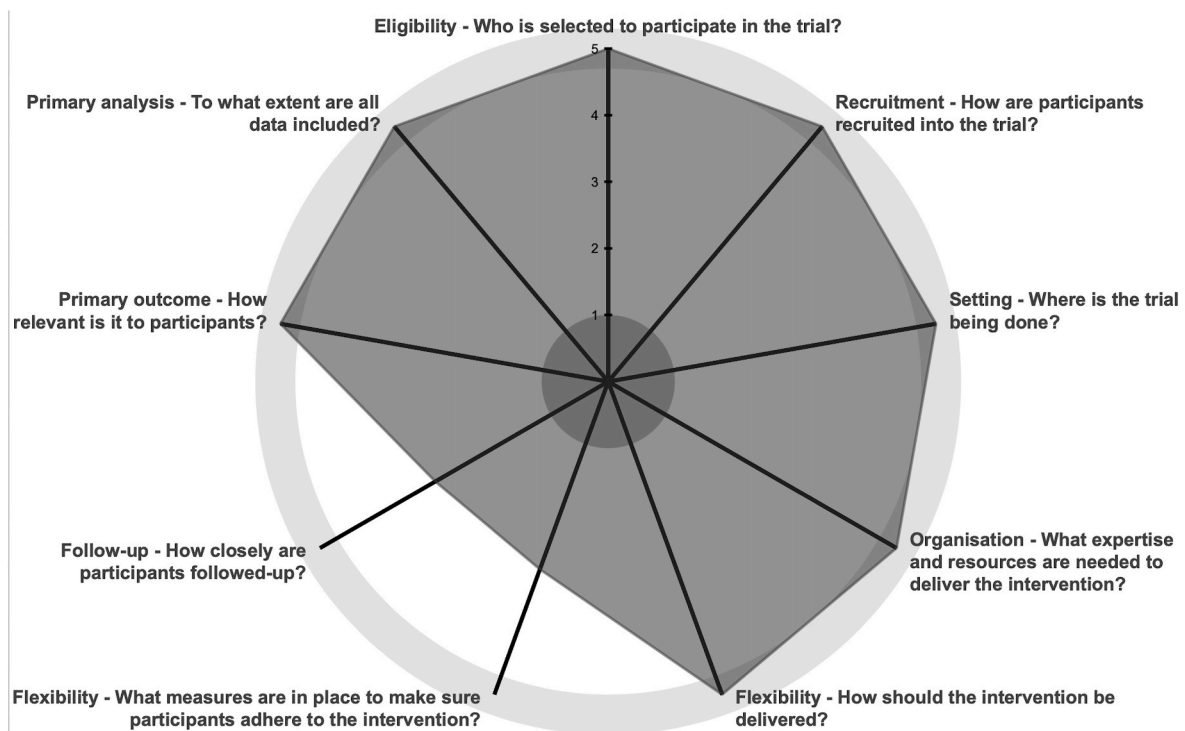


Fig. 2. PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2) scores for this trial.

participants to receive either PT or OMT + PT. The allocation sequence will present 16 blocks of 8 participants each, concealed in sequentially numbered sealed opaque envelopes. Allocation will be performed by social assistant not enrolled in the assessments and blinded to the interventions and blocks. Envelopes will be opened to reveal group allocation immediately before the first session for intervention.

2.6. Blinding

To ensure the expectation of treatment is equally balanced between the groups the participants will not be aware of the study hypothesis regarding the between-group comparisons. It is not possible to blind the clinicians regarding the groups and the participants regarding their treatment. The outcome assessor and statistician will be blind to the allocations of groups.

2.7. Interventions

All patients with long COVID referred to the rehabilitation service will be received by a social assistant to allocate the participants in two groups PT or OMT + PT, present the informed consent form and apply the questionnaires that will be used to assess the groups. The interventions will be conducted according to each patient’s clinical presentation, following their usual care and without creating any changes that could denature the routine clinical practice (Table 1). Participants in both groups are not restricted to access other interventions (e.g., medications or self-guided physical activity). In the follow-up questionnaire they may report other interventions in the last three months if any.

The criteria for discontinuing the treatment in both groups include participants request to withdraw from the research, any condition that prevents the participant from reaching the treatment setting,

Table 1

Characteristics of the interventions for the osteopathic manipulative treatment combined with physiotherapy (OMT + PT) and physiotherapy treatment alone (PT) arms.

Group	PT	PT + OMT
Participants	38	38
Frequency	Maximum of 2 weekly sessions	Maximum of 2 weekly sessions of PT plus maximum of 7 OMT sessions
Duration	8 weeks	8 weeks
Brief description	The physiotherapy approach for patients with long COVID includes motor and respiratory rehabilitation aiming at maintaining and/or improving joint mobility, muscle strength, and functional exercise capacity	Participants will receive OMT in addition to the same interventions of PT group. The OMT entail direct (high-velocity low-amplitude; muscle energy; and myofascial release), indirect (functional techniques and balanced ligamentous tension), visceral, and cranial techniques
Within-session assessment	At each visit, the participants respond by self-report about their general condition. Depending on the case, the physiotherapist will perform a reevaluation with specific tests.	Participants will undergo the same assessments of PT group. Participants will also receive a full-body osteopathic examination which include clinical exams, observation, screening tests, palpation, and motion testing.
Health care team	Five physiotherapists, with more than 5 years of experience each, duly registered with their class council.	In addition to the five physiotherapist, other four osteopaths with more than 5 years of experience each and duly registered with their class council; each participant will be accompanied by the same osteopath.

hospitalization, or death. The number of consultations/appointments for each participant will be recorded, as well as possible absences from scheduled appointments. To reduce attrition rate, on every absence the social worker will contact the participant via phone call to inquire about the reason for the absence and encourages the participant to continue the treatment. In the follow-up questionnaire they may report reasons for dropping out of the trial to be categorized as cost, health improvement, aggravation of symptoms, death, or others (e.g., relatives sickness, no allowance work leave).

2.8. PT group

Participants in this group will receive physiotherapy sessions with a maximum frequency of 2 weekly sessions, as defined by the physiotherapist, according to personalized therapeutic plans for a period of 2 months. The physiotherapy approach includes motor and respiratory interventions aiming at maintaining and/or improving joint mobility, muscle strength, and functional exercise capacity [8]. At each visit, the participants respond by self-report about their general condition. Depending on the case, the physiotherapist will perform a reevaluation with specific tests. The PT group will receive physiotherapy treatment offered by five physiotherapists, with more than 5 years of experience each, duly registered with their class council. The treatment provided will be registered on each participant’s clinical notes and a summary of main interventions will reported.

2.9. OMT + PT group

Participants in this group will receive OMT in addition to the same interventions of PT group for the same 2-month period. The frequency of treatment will be decided based on the clinical judgment of the osteopath who is accompanying each case, not exceeding 7 consultations in total. At each visit, the participants will receive a full-body osteopathic examination which include clinical exams, observation, screening tests, palpation, and motion testing. The OMT entails direct (high-velocity low-amplitude; muscle energy; and myofascial release), indirect (functional techniques and balanced ligamentous tension), visceral, and cranial techniques [36]. Selection of specific OMT will follow the ‘TART’ criteria—Tissue texture changes, Asymmetry, Restriction of motion, Tenderness [12,18,36–38]. OMT will be provided by 4 osteopaths with more than 5 years of experience each and duly registered with the Brazilian register of osteopaths; each participant will be accompanied by the same osteopath.

2.10. Outcome measures and assessment points

The primary outcomes are fatigue and functional status associated with long COVID measured two months after randomization. The secondary outcomes are fatigue, functional status, and global perceived effect three months after randomization. All patients with long COVID referred to the rehabilitation service will be received by a social worker who will present the informed consent form and apply the questionnaires that will be used to assess the groups. The allocation of the participants in two groups PT or OMT + PT will be performed by a research assistant. The physiotherapy and osteopathic providers and assessor roles are separated by using a blinded research assistant. The participants are aware that the social worker will not communicate their symptom report to the provider.

The Fatigue Severity Scale (FSS) aims to assess how impactful is fatigue on activities of daily living and on an individual’s lifestyle. This tool can be used and recommended in various conditions. the scale consists of 9 items on how fatigue interferes with certain activities. Severity is classified according to a self-report scale. The scale consists of a 7-point score where 1 = strongly disagree and 7 = strongly agree. The minimum score is 9 and the maximum is 63. The higher the score is the greater the severity of fatigue [39]. The Portuguese-Brazil version of FSS

has high reliability (Cronbach's alpha = 0.93) and good construct validity with pain and fatigue instruments (Pearson correlation of 0.60 and 0.56, respectively) [40].

The Post-COVID Functional State scale (PCFS) is a questionnaire for the purpose of assessing functional limitations in patients affected by COVID-19. This instrument tries to capture the range of possibilities for functional changes that the virus can cause. PCFS covers limitations of daily tasks/activities at home or at work/school, as well as changes in lifestyle, sports and social activities are also included. The scale has a score from 0 to 4 with 0 being no functional limitation and 4 severe functional limitation (<https://osf.io/qgpdv/>) regarding his condition on the day of application [41]. The Portuguese-Brazil version of PCFS has weak-to-strong construct validity (Pearson correlation in range 0.233–0.661) with health-related quality of life [42].

The Perceived Change Scale (Patient Version) (EMP-patient) scale aims to assess the results of the treatment received from the perspective of the patients themselves. It has 19 items, 18 of which assess the perceived changes related to: occupation and physical health, psychological dimension and sleep, relationships, and emotional stability, in addition to a last item that globally assesses the perceived change. Each item has 3-point Likert responses, where point 1 equates to worse than before, 2 to no change and 3 to better than before [43]. The Portuguese-Brazil version of EMP-patient has good internal consistency (Cronbach alpha = 0.85), test-retest temporal stability (Pearson correlation = 0.93) and convergent construct validity with a service satisfaction instrument (Pearson correlation = 0.37) [44].

2.11. Handling and recording of adverse events

Either physiotherapists or osteopaths providing the interventions will inquire about possible adverse events and this information will be recorded in the patient file. In case of any adverse events the researchers will ensure that the condition is managed and will decide the further course of action based.

2.12. Statistical analysis including sample size calculations

The sample was calculated using the formula for a superiority trial [45]. Sample size was calculated based on a minimal clinical important difference between groups on 1 point (standard deviation of 2.0 points) on the FSS scores at 2 months [46]; no calculation was performed based on PSFS as to the best of our knowledge minimally important differences are yet to be determined [41]. A total sample of 64 participants (32 per arm) is required considering a type-I error of 5% and type-II error of 20%. With a possible 15% loss to follow-up, the required total sample size is 76 participants.

A statistician will conduct the analysis using encoded and deidentified data in R version 4.1.2. The principle of intention-to-treat will be used for analysis [47]. All enrolled participants will be followed through the study and included in the analysis and compared in the outcome measures on the basis of the treatment group to which they were randomly allocated at baseline, regardless of deviations from randomized allocation (e.g., deviated from the treatment protocol, received a different treatment, non-compliance); false inclusions; or missing outcomes (e.g., they started the treatment allocated, subsequently withdrew from the trial, or were lost to follow-up). Sensitivity analysis will be conducted under a per-protocol analysis to test for possible effects of incomplete adherence and loss to follow-up [48]; prerandomization data (age, sex, baseline functional status, time since acute COVID-19 infection, history of ICU admission) will be included as adjustments.

Data will be assessed for evidence of departure from normality and will either be transformed or analyzed using a nonparametric equivalent, if required. Comparative summary statistics (difference in means with 95% confidence intervals) will be reported. Independent mixed linear models will be used to test the interaction and main effects of group (OMT + PT, PT) and time (baseline, 2 months, 3 months) for the

study outcomes (FSS, PCFS, PCS), considering age sex, time since acute COVID-19 infection, and history of ICU admission as covariates. Baseline variables will be evaluated as predictors and moderators of treatment including terms and interaction models [49].

Missing data will be assumed to be missing at random. Multiple imputation will be used to account for these missing data [50]. Missing values in outcome variables will be estimated using multiple imputation by chained equations after 50 replicated imputed data sets. Variables included in the multiple imputation process included factors group, time, and the respective outcome variable.

2.13. Data management

Data will be audited regularly by the statistician for omissions and errors. Data will be double-entered manually and potential divergencies will be resolved. Electronic data will be stored on password-protected servers and paper-form data will be stored in locked filing cabinets, both at the Engenho de Dentro Municipal Rehabilitation Center. Data will only be accessible to the research team. All documented data will be coded using a unique identification number given for each participant after randomization. A secure list of participant identification numbers will be preserved separate from the deidentified data.

3. Discussion

This paper presents a research protocol and rationale for a pragmatic randomized controlled superiority trial to compare the effectiveness of OMT combined with PT as compared to PT alone on fatigue and functional status in adults with long COVID. The reporting of effects of physiotherapy interventions are emerging for patients with long COVID [3], but for OMT remains unknown. Fatigue and functional status are both complex symptoms, being both among the most common and persistent sequelae in long COVID [6]. Likewise, both PT and OMT interventions target multiple dimensions under the biopsychosocial model [3,10–15]. Hence, this study will provide further evidence on the combined effects of OMT and PT on clinically relevant outcomes. These aims highlight the need for a pragmatic trial as both physiotherapy and OMT are currently delivered in the public health setting on a national scale.

Strengths of this protocol include the trial's randomized, pragmatic design; the use of two main physical rehabilitation interventions available in the national public health setting; the implementation of procedures to reduce potential threats to internal validity, such as the blinding (social assistant, professionals delivering the intervention, statistician); computer-based, block randomization of groups; and using valid and reliable instruments for assessing the outcomes. Limitations of this protocol include threats to external validity and generalizability: exclusion of participants with chronic neurologic and musculoskeletal conditions; possible drop-outs and/or non-compliance rates higher than the anticipated; and no measures to assess for the influence of expectation effects (i.e., sensitivity analysis) on the outcomes given the lack of blinding of participants. When completed, we expect this study to contribute to evidence regarding the effectiveness of PT and OMT interventions delivered under pragmatic conditions in the public setting.

Ethical approval

This study was approved by the institutional research ethics committee (38342520.7.0000.5235) following national and regulations and the Declaration of Helsinki. All participants will sign an informed consent form after being informed of the nature of the study and the protocol to be carried out.

Publication plan

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Study completion: July 2023. Submission for publication and reportings: December 2023.

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Declaration of competing interest

The funder had no involvement in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijosm.2022.04.004>.

References

- Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19). *JAMA* 2020;324:782. <https://doi.org/10.1001/jama.2020.12839>.
- Kim L, Garg S, O'Halloran A, Whitaker M, Pham H, Anderson EJ, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US coronavirus disease 2019 (COVID-19)-Associated hospitalization surveillance network (COVID-NET). *Clin Infect Dis* 2020;30:329. <https://doi.org/10.1093/cid/ciaa1012>.
- Silva RMV, Sousa AVC. Chronic phase of COVID-19: challenges for physical therapists in the face of musculoskeletal disorders. *Fisioter Em Mov* 2020;33:2–4. <https://doi.org/10.1590/1980-5918.033.ed02>.
- World Health Organization WHO. *Transmission of SARS-CoV-2: implications for infection prevention precautions*. 2020. Geneva.
- Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun* 2020;87:18–22. <https://doi.org/10.1016/j.bbi.2020.03.031>.
- López-León S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebollo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *SSRN Electron J* 2021;1–22. <https://doi.org/10.2139/ssrn.3769978>.
- Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nat Med* 2021;27:601–15. <https://doi.org/10.1038/s41591-021-01283-z>.
- Thomas P, Baldwin C, Bissett B, Boden I, Gosselink R, Granger CL, et al. Physiotherapy management for COVID-19 in the acute hospital setting: clinical practice recommendations. *J Physiother* 2020;66:73–82. <https://doi.org/10.1016/j.jphys.2020.03.011>.
- Goodwin VA, Allan L, Bethel A, Cowley A, Cross JL, Day J, et al. Rehabilitation to enable recovery from COVID-19: a rapid systematic review. *Physiotherapy* 2021;111:4–22. <https://doi.org/10.1016/j.physio.2021.01.007>.
- Adams J, Sibbritt D, Steel A, Peng W. A workforce survey of Australian osteopathy: analysis of a nationally-representative sample of osteopaths from the Osteopathy Research and Innovation Network (ORION) project. *BMC Health Serv Res* 2018;18:352. <https://doi.org/10.1186/s12913-018-3158-y>.
- Alvarez G, Roura S, Cerritelli F, Esteves JE, Verbeeck J, van Dun PLS. The Spanish Osteopathic Practitioners Estimates and RATES (OPERA) study: a cross-sectional survey. *PLoS One* 2020;15:e0234713. <https://doi.org/10.1371/journal.pone.0234713>.
- Seffinger MA. *Foundations of osteopathic medicine: philosophy, science, clinical applications, and research*. fourth ed. Lippincott Williams and Wilkins; 2018.
- Steel A, Peng W, Sibbritt D, Adams J. Introducing national osteopathy practice-based research networks in Australia and New Zealand: an overview to inform future osteopathic research. *Sci Rep* 2020;10:846. <https://doi.org/10.1038/s41598-020-57918-7>.
- van Dun PLS, Kouwenberg T. *The scope of osteopathic practice in Europe*. 2012. Brussels.
- World Health Organization WHO. *Benchmarks for training in traditional/complementary and alternative medicine: benchmarks for Training in Osteopathy*. Geneva: World Health Organization; 2010.
- Marin T, Maxel X, Robin A, Stubbe L. Evidence-based assessment of potential therapeutic effects of adjunct osteopathic medicine for multidisciplinary care of acute and convalescent COVID-19 patients. *Explore* 2021;17:141–7. <https://doi.org/10.1016/j.explore.2020.09.006>.
- Hruby RJ, Hoffman KN. Avian influenza: an osteopathic component to treatment. *Osteopath Med Prim Care* 2007;1:10. <https://doi.org/10.1186/1750-4732-1-10>.
- Cerritelli F, Carinci F, Pizzolorusso G, Turi P, Renzetti C, Pizzolorusso F, et al. Osteopathic manipulation as a complementary treatment for the prevention of cardiac complications: 12-Months follow-up of intima media and blood pressure on a cohort affected by hypertension. *J Bodyw Mov Ther* 2011;15:68–74. <https://doi.org/10.1016/j.jbmt.2010.03.005>.
- Müller A, Franke H, Resch K-L, Fryer G. Effectiveness of osteopathic manipulative therapy for managing symptoms of irritable bowel syndrome: a systematic review. *J Osteopath Med* 2014;114:470–9. <https://doi.org/10.7556/jaoa.2014.098>.
- Dal Farra F, Risio RG, Vismara L, Bergna A. Effectiveness of osteopathic interventions in chronic non-specific low back pain: a systematic review and meta-analysis. *Compl Ther Med* 2021;56:102616. <https://doi.org/10.1016/j.ctim.2020.102616>.
- de Zoete A, de Boer MR, Rubinstein SM, van Tulder MW, Underwood M, Hayden JA, et al. Moderators of the effect of spinal manipulative therapy on pain relief and function in patients with chronic low back pain: an individual participant data meta-analysis. *Spine (Phila Pa 1976)* 2021;46:E505–17. <https://doi.org/10.1097/BRS.0000000000003814>.
- Rubinstein SM, de Zoete A, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2019;364:l689. <https://doi.org/10.1136/bmj.l689>.
- Noll DR, Degenhardt BF, Johnson JC. Multicenter osteopathic pneumonia study in the elderly: subgroup analysis on hospital length of stay, ventilator-dependent respiratory failure rate, and in-hospital mortality rate. *J Am Osteopath Assoc* 2016;116:574–87. <https://doi.org/10.7556/jaoa.2016.117>.
- Lesho E, McKeown A, Laguio-Vila M. The rationale for including osteopathic manipulative treatment in the management of infections: a hermeneutic review. *Expert Rev Anti Infect Ther* 2021;1–9. <https://doi.org/10.1080/14787210.2021.1935236>.
- Karshikoff B, Sundelin T, Lasselin J. Role of inflammation in human fatigue: relevance of multidimensional assessments and potential neuronal mechanisms. *Front Immunol* 2017;8:1–12. <https://doi.org/10.3389/fimmu.2017.00021>.
- Cicchitti L, Martelli M, Cerritelli F. Chronic inflammatory disease and osteopathy: a systematic review. *PLoS One* 2015;10:1–18. <https://doi.org/10.1371/journal.pone.0121327>.
- Keefe FJ, Jensen MP, Williams ACdC, George SZ. The yin and yang of pragmatic clinical trials of behavioral interventions for chronic pain. *Publish Ah*; 2021. <https://doi.org/10.1097/j.pain.0000000000002546>. Pain.
- Galeoto G, Sansoni J, Valenti D, Mollica R, Valente D, Parente M, et al. The effect of physiotherapy on fatigue and physical functioning in chronic fatigue syndrome patients: a systematic review. *Clin Ter* 2018;169:e184–8. <https://doi.org/10.7417/T.2018.2076>.
- Wiegand S, Bianchi W, Quinn TA, Best M, Fotopoulos T. Osteopathic manipulative treatment for self-reported fatigue, stress, and depression in first-year osteopathic medical students. *J Am Osteopath Assoc* 2015;115:84–93. <https://doi.org/10.7556/jaoa.2015.019>.
- Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwahlenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ* 2015;350. <https://doi.org/10.1136/bmj.h2147>. h2147–h2147.
- Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. <https://doi.org/10.1136/bmj.e7586>.
- Altman DG. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663. <https://doi.org/10.7326/0003-4819-134-8-200104170-00012>.
- Boutron I, Altman DG, Moher D, Schulz KF, Ravaut P. CONSORT statement for randomized trials of nonpharmacologic treatments: a 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. *Ann Intern Med* 2017;167:40. <https://doi.org/10.7326/M17-0046>.
- Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348. <https://doi.org/10.1136/bmj.g1687>. g1687–g1687.
- Raveendran AV. Long COVID-19: challenges in the diagnosis and proposed diagnostic criteria. *Diabetes Metab Syndr Clin Res Rev* 2021;15:145–6. <https://doi.org/10.1016/j.dsx.2020.12.025>.
- Giusti R. *Glossary of osteopathic terminology*. third ed. American Association of Colleges of Osteopathic Medicine; 2017.
- Pizzolorusso G, Turi P, Barlafante G, Cerritelli F, Renzetti C, Cozzolino V, et al. Effect of osteopathic manipulative treatment on gastrointestinal function and length of stay of preterm infants: an exploratory study. *Chiropr Man Ther* 2011;19:15. <https://doi.org/10.1186/2045-709X-19-15>.
- Basile F, Scionti R, Petracca M. Diagnostic reliability of osteopathic tests: a systematic review. *Int J Osteopath Med* 2017;25:21–9. <https://doi.org/10.1016/j.ijosm.2017.03.004>.
- Krupp LB. The fatigue severity scale. *Arch Neurol* 1989;46:1121. <https://doi.org/10.1001/archneur.1989.00520460111022>.
- Toledo FO, Junior WM, Speciali JG, Sobreira CFDR. PND66 cross-cultural adaptation and validation of the Brazilian version of the fatigue severity scale (FSS). *Value Health* 2011;14:A329–30. <https://doi.org/10.1016/j.jval.2011.08.532>.
- Klok FA, Boon GJAM, Barco S, Endres M, Miranda Geelhoed JJ, Knauss S, et al. The post-COVID-19 functional status scale: a tool to measure functional status over time after COVID-19. *Eur Respir J* 2020;56. <https://doi.org/10.1183/13993003.01494-2020>.
- Machado FVC, Meys R, Delbressine JM, Vaes AW, Goërtz YMJ, van Herck M, et al. Construct validity of the post-COVID-19 functional status scale in adult subjects with COVID-19. *Health Qual Life Outcome* 2021;19:40. <https://doi.org/10.1186/s12955-021-01691-2>.

- [43] Perreault M, White ND, Fabrès É, Landry M, Anestin AS, Rabouin D. Relationship between perceived improvement and treatment satisfaction among clients of a methadone maintenance program. *Eval Progr Plann* 2010;33:410–7. <https://doi.org/10.1016/j.evalprogplan.2009.12.003>.
- [44] Bandeira MB, Andrade MCR, Costa CS, Silva MA. Percepção dos pacientes sobre o tratamento em serviços de saúde mental: validação da Escala de Mudança Percebida. *Psicol Reflexão Crítica* 2011;24:236–44. <https://doi.org/10.1590/S0102-79722011000200004>.
- [45] Christensen E. Methodology of superiority vs . equivalence trials and non-inferiority trials. *Stat Med* 2007;26:947–54. <https://doi.org/10.1016/j.jhep.2007.02.015>.
- [46] Nordin Å, Taft C, Lundgren-Nilsson Å, Dencker A. Minimal important differences for fatigue patient reported outcome measures—a systematic review. *BMC Med Res Methodol* 2016;16:62. <https://doi.org/10.1186/s12874-016-0167-6>.
- [47] Armijo-Olivo S, Warren S, Magee D. Intention to treat analysis, compliance, drop-outs and how to deal with missing data in clinical research: a review. *Phys Ther Rev* 2009;14:36–49. <https://doi.org/10.1179/174328809X405928>.
- [48] Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. *N Engl J Med* 2017;377:1391–8. <https://doi.org/10.1056/NEJMs1605385>.
- [49] West BT, Galecki AT. An overview of current software procedures for fitting linear mixed models. *Am Statistician* 2011;65:274–82. <https://doi.org/10.1198/tas.2011.11077>.
- [50] Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;339:157–60. <https://doi.org/10.1136/bmj.b2393>.