STUDY PROTOCOL

Addressing post-COVID-19 musculoskeletal symptoms through pulmonary rehabilitation and telemedicine: A study protocol [version 3; peer review: 2 approved, 1 approved with reservations]

Previously titled: Addressing post-COVID-19 musculoskeletal symptoms through telemedicine: A study protocol

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Abstract

Objective

The purpose of the study will be to evaluate the effect of pulmonary rehabilitation on the improvement of patients with post-COVID-19 musculoskeletal symptoms, as well as to quantify the impact of telemedicine that evaluates the evolution of pain, functionality, and quality of life.
Methods

We will carry out a case-control study in post-COVID-19 musculoskeletal symptoms patients who will undergo pulmonary rehabilitation, together with an intervention and a follow-up using programmed telemedicine sessions. Data will be collected on the improvement of functional capacity and quality of life, in addition to assessing the evolution of musculoskeletal symptomatology, as well as pain and psychological variables. The approaches of face-to-face rehabilitation and telerehabilitation will also be compared. The telemedicine sessions will improve user adherence and follow-up, and the results are expected to be disseminated to the scientific community during and after the end of the study.

Keywords
COVID-19; Pain; SARS-CoV-2; Musculoskeletal Disease; Telemedicine

This article is included in the Health Services gateway.

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Author roles: Sánchez Romero EA: Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Fernández Carnero J: Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Alonso Pérez JL: Funding Acquisition, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Martínez Rolando L: Data Curation, Formal Analysis, Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; Villafañe JH: Conceptualization, Formal Analysis, Investigation, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: Award for Best Research Project in post-COVID-19 sequelae awarded by the Ilustre Colegio Profesional de Fisioterapeutas de la Comunidad de Madrid (Spain), December 2021. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Sánchez Romero EA, Fernández Carnero J, Alonso Pérez JL et al. Addressing post-COVID-19 musculoskeletal symptoms through pulmonary rehabilitation and telemedicine: A study protocol [version 3; peer review: 2 approved, 1 approved with reservations] F1000Research 2024, 11:898 https://doi.org/10.12688/f1000research.122843.3

First published: 04 Aug 2022, 11:898 https://doi.org/10.12688/f1000research.122843.1
Introduction

COVID-19 infection causes various clinical manifestations in patients, including neurological manifestations, ranging from headache, dizziness, neuralgia, and neuropathy, to musculoskeletal symptoms and myalgia. Some of the most commonly reported symptoms of COVID-19 include fatigue, cough, fever, ageusia (loss of taste), anosmia (loss of smell), and dyspnea (shortness of breath). In addition to these symptoms, some people may experience a headache, chest pain, or palpitations. Musculoskeletal alterations cause pain symptoms in COVID-19 patients, appearing to be similar in all countries. Individuals with post-COVID-19 pain experience widespread pain due to altered nociceptive processing. Prolonged immobilization and mechanical ventilation (MV), as well as the restoration of respiratory and physical functions, may delay the patient’s discharge from the intensive care unit (ICU), or only achieve a partial recovery, resulting in decreased quality of life. ICU-acquired weakness (ICUW) impairs the peripheral skeletal and respiratory muscles of critically ill patients. This is one of the most serious consequences of long-term immobilization, resulting in delayed weaning from MV and prolonged hospital stay. It has been described that patients hospitalized for COVID-19 infection presented with mild to moderate generalized pain that resembled the pattern of musculoskeletal pain (myalgias or COVID-19-induced muscle pain). Therefore, understanding the presence and origin of possible sequelae experienced by post-COVID-19 patients should be an emerging priority for researchers and clinicians. Based on these underlying mechanisms of COVID-19 infection, it is very plausible that one of the possible post-COVID-19 outcomes is the development of chronic pain. Chronic pain represents another pandemic crisis in modern society due to its high burden and high prevalence within the general population. Few data are available on post-COVID-19 sequelae related to the development of pain and potential musculoskeletal repercussions, in contrast to research highlighting other dimensions of health. In this context, rehabilitation should be initiated immediately after the acute phase to avoid the progression of hospital-acquired weakness and to achieve rapid functional recovery. The pathogenesis of widespread musculoskeletal pain in COVID-19 survivors remains unclear and possibly involves the peripheral and central nervous systems.

Addressing these sequelae, early exercise and rehabilitation protocols applied during the patient’s hospitalization and after discharge from the hospital can help improve musculoskeletal pain symptoms and prevent functional deterioration. Physical activity with multicomponent programs has been shown to have a positive effect on function and weakness in COVID-19 infected patients, in addition to producing improvements in pain. COVID-19 has a clear functional impairment among other comorbidities.

Pulmonary Rehabilitation (PR), initially for Chronic Obstructive Pulmonary Disease (COPD), is now integral for various chronic cardiopulmonary conditions, involving patient assessment, tailored exercise, education, and behavioral changes. PR includes endurance and resistance training to improve exercise tolerance, quality of life, and reduce hospital admissions, and can be effectively delivered via telerehabilitation, offering practical and cost-efficient benefits.
The use of telemedicine improves physiotherapy care by assessing musculoskeletal disorders, as well as allowing better dissemination of knowledge by improving access for users who cannot frequently attend their face-to-face sessions or to reinforce therapeutic adherence. It facilitates an active role of users, based on personalized risk assessment (biopsychosocial factors), and allows users to be tracked, obtaining data.

The use of Big Data in health tools opens a great opportunity to move toward monitoring platforms that can offer a more complete, adapted, and updated interaction with the user, under the basis of “more users, more data, and then better feedback that allows personalized care”. Likewise, telemedicine makes it possible to improve the information available on health and self-care. The interactive environment aims to create a friendly treatment and learning environment, in addition to improving patient adherence and compliance, as this is directly related to treatment efficacy and preventive actions.

Therefore, the hypothesis will be that post-COVID-19 patients with musculoskeletal symptoms undergoing a rehabilitation program plus telemedicine results in decreased pain and improves functionality and quality of life.

The purpose of the study will be to evaluate the effect of a pulmonary rehabilitation on the improvement of patients with post-COVID-19 musculoskeletal symptoms, as well as to quantify the impact of telemedicine that evaluates the evolution of pain, functionality, and quality of life. The approaches of face-to-face rehabilitation and telerehabilitation will also be compared.

We will also determine the increase in adherence to treatment through the application of telemedicine in post-COVID-19 patients with musculoskeletal symptoms.

**Protocol**

**Study design**

A case-control study will be carried out between June 2022 and February 2023 with male and female patients impacted by post-COVID-19 musculoskeletal symptoms who will undergo a multicomponent rehabilitation program, together with an intervention and a follow-up using programmed telemedicine sessions. Procedures will be conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and checklist. The study protocol has been approved by the Ethical Committee of the European University of Madrid (reference number CIPI/21/046). Written informed consent will be obtained from all participants and all procedures were conducted according to the Declaration of Helsinki.

Pulmonary Rehabilitation will be carried out in six weeks of intervention with two weekly face-to-face sessions that will include endurance and resistance exercises (Figure 1) for both groups (case and control). A once a week telemedicine session will be carried out with the case group only before the face-to-face sessions, consisting of education, respiratory exercise, mobility and stretching, giving them a place to provide feedback and re-evaluate patients mid-treatment (Figure 2) and will be aimed at assessing improvement and improving therapeutic adherence. The same protocol will be performed once a week in the control group prior to the face-to-face sessions so that comparisons can be made between the two groups. This protocol will be characterized by being progressive and individualized by monitoring the load with validated tools such as the modified Borg scale and Karvonen’s formula.

**Participants**

All participants, whether or not they were previously admitted to ICU by COVID-19, will be contacted by telephone to propose their participation in the study, after which the selected sample meeting the criteria described below that signs the informed consent will be assessed via a comprehensive clinical anamnesis and objective physical examination performed.
by two expert physical therapists of the rehabilitation department of the Rey Juan Carlos University Hospital of Móstoles, Madrid, Spain, between June 2022 and October 2022. To be included in the study, the patients need to be post-COVID-19 patients (ICU or non-ICU) with musculoskeletal symptoms and be of adult age (over 18 years): patients experiencing widespread muscle and joint pain due to altered nociceptive processing from a post-COVID-19 condition. Exclusion criteria included: myocardial infarction, uncontrolled arrhythmia, recent pulmonary thromboembolism, terminal illness, patients undergoing lower limb unloading, lower or upper limb fractures in the last three months, severe pain (score greater than 7 on the VAS of 10 points), suffering from the previous pathology that causes neuromuscular weakness, be younger than 18 and older than 65 years old, influenced by medication that does not allow assessment of the real muscular functionality of the patient, patients with cognitive impairment that would prevent them from understanding and collaborating in the performance of the PR program plus telemedicine, patients with cardiorespiratory instability and
uncontrolled arterial hypertension, systemic illness (tumor and rheumatologic diseases), recent unrelated trauma, and limiting psychiatric pathology.

The group of cases and the group of controls will have identical or similar characteristics, except that the cases will be treated with PR plus telemedicine, and the control group with PR and the same protocol of telemedicine in face-to-face sessions. All subjects will sign an informed consent before inclusion (flowchart, Figure 3).

Allocation concealment and blinding of researchers
In this case-control study, 120 patients (of desired homogeneous distribution of males and females) will be included and classified into the following two groups. The initial and final assessment of each potential study participant will be performed by two investigators outside each participant’s intervention group, another investigator will consider the exclusion criteria and follow the algorithm for detecting samples that are not telemedicine-prone (Figure 4) to stratify the data. An independent researcher with statistical expertise will conduct the analysis of the results obtained.

Clinical measurements
Patients included in the study will be assessed pre- and post-intervention, using the tools and questionnaires found at https://doi.org/10.17605/OSF.IO/2T3JG in Table 1.

Manual grip strength
Grip strength will be measured in the affected hand and in the healthy hand (measuring the maximum grip strength). For this measurement, Handgrip strength averaging the result of three attempts with the dominant hand using a Baseline© model pear dynamometer.

Quality of life
Quality of life will be measured with EuroQol-5D-5L: a test where mobility, self-care, activities of daily living, pain/discomfort and anxiety/depression are assessed.

Activities of daily living
Activities of daily living (ADL) will be measured with the Barthel Index, which assesses the level of independence of the subject with respect to the performance of some ADL’s.

Assessment of exercise capacity
Exercise capacity will be measured with a six-minute walking test (6MWT), a sub-maximal exercise test which consists of the patient walking for six minutes along a 30-meter corridor with two cones marking the distance to be covered while being given a series of cues and monitored for oxygen saturation, heart rate and perceived exertion.

Assessment of motor impairment
Motor impairment will be measured with the Berg Balance Scale (BBS). It determines the ability or inability to safely balance during a series of predetermined tasks.
Assessment of perceived pain

Perceived pain will be measured with the Numerical Pain Rating Scale (NPRS), which measures pain intensity.

Assessment of neuropathic pain

Neuropathic pain will be measured with DN4, a questionnaire that assesses the presence of neuropathic pain.33

Widespread pain

This will be classified as a continuous numerical variable measured by the Widespread Pain Index (WPI). In this index, the patient must mark with an x the areas in which he/she has presented pain during the last week.

Psychological variables and self-efficacy

We will measure psychological variables related to pain sensitivity and other main signs and symptoms, such as kinesiophobia34 and self-efficacy.24,35,36 For this purpose, we will use the Chronic Pain Self-Efficacy Questionnaire, in its Spanish-validated version37 and the Tampa Scale of Kinesiophobia, also translated and validated in Spanish.38 Finally, with Beck Depression Inventory (BDI): scale that allows us to measure depressive symptoms and severity of depression in patients older than 13 years.39

Modulating variables

These variables will be measured by being able to predict a change in the primary measurement results between the first and second measurement of the results or data collection, to facilitate this, the repository found at https://doi.org/10.17605/OSF.IO/2T3JG shows Table 2.

- Employment status: refers to the subject’s current employment status, and will be classified as a nominal qualitative variable, with the following response modalities: “active”, “unemployed with benefits”, “unemployed without benefits”, “pensioner”.

- Levels of physical exercise measures the average amount of physical exercise currently performed per week, and will be classified as a nominal qualitative variable, with the following response modalities: “none”, “less than three times per week”, “three times per week”, “more than three times per week”.

- Family economic situation: this variable assesses the average annual economic income of the family unit, and is a nominal qualitative variable, with the following response modalities: “more than 40,000 euros”, between 12,000 euros and 40,000 euros”, “less than 12,000 euros”.

- COVID-19’s (SARS-CoV-2) own condition: this variable refers to the current or past presence/absence of illness due to COVID-19 in the subject; it is a nominal qualitative variable, whose response modalities are: “no”, “yes (without symptoms)”, “yes (with symptoms/without admission)”, “yes (with symptoms/admission to ward)”, “yes (with symptoms/admission to ICU)”.

- Loss of family members due to COVID-19 (SARS-Cov-2): refers to the loss of family members in subjects due to COVID-19 disease, being classified as a qualitative dichotomous “yes/no” variable.

- Chronicity: refers to the number of months that the subjects in the sample have been suffering from symptoms, so it will be classified as a continuous quantitative variable.

- Medication: refers to the number of drugs used in the treatment of pain, so it will be classified as a continuous quantitative variable.

Data analysis

SPSS (RRID:SCR_002865) version 25.0 (IBM SPSS Statistics for Windows; Armonk, NY, USA: IBM Corp) and an α error of 0.05 (95% confidence interval) and a desired power of 80% (β error of 0.2) will be used for statistical analysis. The Shapiro-Wilk test and visual distribution will be used to assess deviations from normality. Parametric analysis will be used in case of normality, given the expected sample size. Then, a comparison of both sociodemographic data and main
outcomes between case and control groups will be performed. For case and control groups and for sex, Fisher’s exact test will be used. Pearson’s Chi-square test will compare between case and control groups. In addition, Student’s t-test for independent samples will be used for age and outcomes of the measured variables, and sex and age group. Box plots will be used to illustrate the values of the measured variables of the case and control groups. Univariate correlation analysis will be performed using Pearson’s coefficient (r) to assess the relationship between the variables. Correlations will be interpreted as weak (0.00–0.40), moderate (0.41–0.69) or strong (0.70–1.00). In addition, a multivariate predictive analysis will use linear regression and regression trees. Linear regression will be performed using a stepwise selection method and the R2 coefficient to establish quality adjustments. The sample size will be determined by the number of patients admitted to the hospital between June 2022 and February 2023.

Discussion
Clinical symptoms associated with COVID-19 mainly affect to the respiratory tract, but they manifest heterogeneously from other organ systems including the nervous system. We hypothesize that these patients with post-COVID-19 sequelae will demonstrate a pain and potential musculoskeletal repercussions. We expect to find, that the post-COVID-19 sequelae mechanisms might be a feature of this post-COVID-19 population.

This is the first study to use the telemedicine in post-COVID-19 patients with musculoskeletal symptoms. The results of this study can be implemented in clinical practice to help clinicians deal with this challenging patient population. Furthermore, the research will allow the extraction of data on the different patient profiles, symptoms and post-COVID-19 sequelae, in addition to the different risk factors affecting post-COVID-19 patients with musculoskeletal symptoms.

Giacalone et al. detailed how COVID-19 may invade the central nervous system (CNS) via the viremic spread of SARS-CoV-2, allowing the virus to reach the brain and break through the blood-brain barrier. They also comment on how acute cerebrovascular diseases, such as ischemic and hemorrhagic strokes, have been observed with a higher incidence in patients with severe coagulopathies. Encephalitis, meningitis, seizures, and disseminated acute encephalomyelitis have also been reported in COVID-19 patients. Additionally, peripheral nervous system (PNS) involvement may include myalgia and muscle fatigue, changes in smell, taste, and chemesthetic function, and rare cases of Guillain-Barré syndrome.

In a recent review, Giacalone et al. detailed how there is evidence to support the use of telemedicine during the COVID-19 pandemic and its potential for permanent integration into healthcare. They assert that telemedicine offers practical and cost-effective advantages, such as breaking down geographic and time barriers, reducing waiting lists, and saving on national healthcare spending.

Patients with chronic pain (20% of the population) have many issues to deal with as there is limited access to specialised pain management centres. Post COVID-19 patients with persistent pain are at risk of not receiving the required recognition and attention by the healthcare system and therefore they will not receive the most optimal pain management for this new pain syndrome. The social repercussions of the current project are imminent since the world should be prepared for a large number (probably millions) of COVID-19 survivors with potential post COVID-19 pain sequelae.

Various studies highlight the efficacy of Face-to-Face PR and Telerehabilitation in improving health status in lung diseases, including COVID-19, with Telerehabilitation showing positive clinical outcomes compared to traditional interventions. However, a recent meta-analysis comparing Face-to-Face PR and Telerehabilitation in patients with post-COVID-19 found no significant difference in health status improvement, indicating the need for tailored approaches and consideration of patient barriers in implementing telerehabilitation programs. The improvement of adding telerehabilitation may be due to the monitoring and personal contact with the patient.

Conclusions
This project aims to demonstrate that PR approach to musculoskeletal sequelae of COVID-19 will improve pain, functionality and quality of life, achieving through telemedicine sessions an improvement in therapeutic adherence and follow-up. The approaches of face-to-face rehabilitation and telerehabilitation will also be compared. The results are expected to be disseminated to the scientific community during and after the end of the study.

Author contributions
Conceptualization, J.H.V. and E.A.S.R.; methodology, J.H.V., L.M.R. and E.A.S.R.; software, J.H.V.; validation, all authors; formal analysis, J.F.C., E.A.S.R., L.M.R., and J.H.V.; investigation, all authors; resources, J.L.A.P.; writing—original draft preparation, J.H.V, J.F.C., L.M.R. and E.A.S.R.; writing—review and editing, E.A.S.R., J.F.C., L.M.R. and J.H.V.; visualization, E.A.S.R., L.M.R. and J.H.V.; supervision, all authors; project administration,
E.A.S.R., L.M.R. and J.H.V.; funding acquisition, E.A.S.R. and J.H.V. All authors have read and agreed to the published version of the manuscript.

Data availability

Underlying data

No data are associated with this article.

Extended data

Extended data for ‘Addressing post-COVID-19 musculoskeletal symptoms through telemedicine: A study protocol’ https://doi.org/10.17605/OSF.IO/2T3JG contains the following data:

- **Table 1.** Baseline descriptive and clinical variables in the total sample previous intervention

- **Table 2.** Baseline predictive variables in the total sample previous intervention

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Acknowledgments

This study is supported by the Italian Ministry of Health-Ricerca Corrente 2021.

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This study is supported by the Italian Ministry of Health-Ricerca Corrente 2021.

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Open Peer Review

Current Peer Review Status:  

Version 3

Reviewer Report 30 April 2024

https://doi.org/10.5256/f1000research.164182.r261883

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I appreciate the authors’ efforts to address the feedback provided in the previous review. As the revisions are indeed substantial and address the concerns raised earlier, I approve the new version of the article.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Rheumatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 21 March 2024

https://doi.org/10.5256/f1000research.147632.r251240

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The study aims to investigate the effectiveness of a multicomponent rehabilitation program combined with telemedicine in improving pain, functionality, and quality of life in post-COVID-19 patients with musculoskeletal symptoms.

- **Structured methodology:** The protocol outlines a case-control design with clear inclusion and exclusion criteria for participants.
- **Telemedicine integration:** The study explores the potential of telemedicine for delivering rehabilitation programs and improving adherence in this patient population.
- **Data analysis plan:** The researchers describe a comprehensive statistical analysis plan using appropriate tests based on data types.
- **Potential impact:** The findings could inform clinical practice for managing post-COVID-19 musculoskeletal symptoms and contribute to the integration of telemedicine in rehabilitation.

However, some points need to be considered.

- The title doesn't refer to rehabilitation which is one of the main objectives of the study.
- The objectives should be mentioned at the end of the introduction.
- In the introduction, it would be better to give more information regarding telemedicine (what is meant by telemedicine, how it is conducted,...).
- The patients included in the study have post-COVID 19 musculoskeletal symptoms, but no clarification is given to what they meant by musculoskeletal symptoms.
- The authors mentioned that “the group of cases and the group of controls will have identical or similar characteristics, except that the cases will be treated with the multicomponent rehabilitation program plus telemedicine, and the control group with the multicomponent rehabilitation”, so the group of cases should have a different study protocol which consists of “education, respiratory exercise, mobility, and stretching, giving them a place to provide feedback and re-evaluate patients mid-treatment.” In this situation, will the group that doesn’t receive telemedicine also not have “education, respiratory exercise, mobility, and stretching, giving them a place to provide feedback and re-evaluate patients mid-treatment”? If not, the study groups cannot be compared.
- Blinding participants and researchers might be challenging due to the nature of the intervention (telemedicine sessions).
- While telemedicine use in rehabilitation is growing, the overall approach of combining rehabilitation with telemedicine for post-COVID-19 musculoskeletal problems might not be entirely novel.
- The six-week intervention period might be insufficient to observe long-term effects on chronic pain and functional limitations.
- The discussion section could be expanded to address potential mechanisms by which telemedicine might improve outcomes.
- The authors might consider including cost-effectiveness analysis alongside clinical outcomes.
- The study plans to recruit from a single center, potentially limiting the generalizability of findings to broader populations.

**Is the rationale for, and objectives of, the study clearly described?**
Yes

**Is the study design appropriate for the research question?**
Partly

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: rheumatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 23 Mar 2024

Eleuterio A. Sánchez Romero

Dear reviewer,

Thank you for reading through our manuscript giving us constructive feedback and pointing out important details. The revision process has made the manuscript clearer.

1. The title doesn't refer to rehabilitation which is one of the main objectives of the study.
Response: Thank you for your comment. The title has been modified as suggested.

2. The objectives should be mentioned at the end of the introduction.
Response: The sentence corresponding to the objectives of the study has been added at the end of the Discussion section. Thank you.

3. In the introduction, It would be better to give more information regarding telemedicine (what is meant by telemedicine, how it is conducted, ...).
Response: A new paragraph has been added in the Introduction section regarding this, in addition to further detailing the telerehabilitation protocol in the Methods section. Thank you.

4. The patients included in the study have post-COVID 19 musculoskeletal symptoms, but no clarification is given to what they meant by musculoskeletal symptoms.
Response: The required clarification has been added to the Methods section (inclusion and exclusion criteria). Thank you very much.

5. The authors mentioned that “the group of cases and the group of controls will have identical or similar characteristics, except that the cases will be treated with the multicomponent
rehabilitation program plus telemedicine, and the control group with the multicomponent rehabilitation**, so the group of cases should have a different study protocol which consists of “education, respiratory exercise, mobility, and stretching, giving them a place to provide feedback and re-evaluate patients mid-treatment.” In this situation, will the group that doesn’t receive telemedicine also not have “education, respiratory exercise, mobility, and stretching, giving them a place to provide feedback and re-evaluate patients mid-treatment”? If not, the study groups cannot be compared.

Response: Thank you for your comment. Due to your comment, the information in the corresponding section has been modified, clarifying that both groups will receive pulmonary rehabilitation, and in addition, the same telemedicine protocol will be executed in face-to-face mode for the group that is not treated with telemedicine.

6. Blinding participants and researchers might be challenging due to the nature of the intervention (telemedicine sessions).

Response: Thank you for your comment. In the section "Allocation concealment and blinding of investigators", the single blinding of evaluators is detailed, although it is also detailed that case subjects will not know the treatment of controls, and vice versa.

7. While telemedicine use in rehabilitation is growing, the overall approach of combining rehabilitation with telemedicine for post-COVID-19 musculoskeletal problems might not be entirely novel.

Response: Thank you for your comment. You are absolutely right in your statement, since it has been some time since the publication of our protocol. However, and although there are only a few weeks left for the submission of the manuscript to a journal, the authors think that the part of having generated post-COVID-19 patient profiles thanks to the use of Big Data, will offer interesting models that will help to better understand the disease.

8. The six-week intervention period might be insufficient to observe long-term effects on chronic pain and functional limitations.

Response: Thank you for your comment. It is true what you detail, and although we can no longer modify the protocol because the intervention phase of the study has already ended, the authors will add this point as a limitation in the manuscript submitted to the journal.

9. The discussion section could be expanded to address potential mechanisms by which telemedicine might improve outcomes.

Response: Thank you for your comment. A paragraph has been added in the discussion regarding this.

10. The authors might consider including cost-effectiveness analysis alongside clinical outcomes.

Response: The authors did not want to add more variables in this study. However, a detailed cost-effectiveness study published by the authors of this study will be presented in the April/June 2024
11. The study plans to recruit from a single center, potentially limiting the generalizability of findings to broader populations.

Response: Thank you for your comment. It is true what you detail, and although we can no longer modify the protocol because the intervention phase of the study has already ended, the authors will add this point as a limitation in the manuscript submitted to the journal.

**Competing Interests:** No competing interests were disclosed.
However, these two references are only suggestions/examples and the authors should be free to search for other similar articles.

Other suggestions:
- Please describe the full names of all acronyms/abbreviations on their first appearance in the text of the manuscript.
- Please make it clear when COVID-19 (the disease) or SARS-CoV-2 (the virus) should be used.
- There are some typographical errors. Please review this.

References
1. Giacalone M, Tovani-Palone MR, Marin L, Febbi M, et al.: Neurological and neuropsychiatric disorders associated with COVID-19. Part I: overview and neurological disorders. *Einstein (Sao Paulo)*. 2021; 19: eCE6448 PubMed Abstract | Publisher Full Text
2. Giacalone A, Marin L, Febbi M, Franchi T, et al.: eHealth, telehealth, and telemedicine in the management of the COVID-19 pandemic and beyond: Lessons learned and future perspectives. *World J Clin Cases*. 2022; 10 (8): 2363-2368 PubMed Abstract | Publisher Full Text

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Public and Global Health, General Medicine.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 28 Apr 2023

Eleuterio A. Sánchez Romero

This is an interesting and very well written study protocol on the treatment of post-COVID-19 musculoskeletal symptoms through telemedicine. The article is relevant and represents an important intellectual contribution to the literature. The methods used are appropriate and the description of the protocol is complete and
quite clear for readers. Furthermore, the proposed objectives are relevant especially for the field of COVID-19. I really appreciate how the authors have described in detail and carefully the design of the protocol as well as all the pertinent methodology. The wisdom and accuracy in the description of data analysis is also another highlight. However, I consider that the discussion could be described in more detail, including new insights. I send below some suggestions that should be especially helpful in generating new ideas and refinement of the manuscript.

Reference suggestions:
PMID: 34730705 PMCID: PMC8528447 - I recommend this reference given that the article provides an important discussion on the neurological findings of COVID-19.

PMID: 35434056 PMCID: PMC8968610 - I recommend this reference given that the article provides an overview of the importance of health, telehealth, and telemedicine for managing COVID-19 patients.
However, these two references are only suggestions/examples and the authors should be free to search for other similar articles.

*Response: Thank you for reading through our manuscript. The “Discussion” section has been restructured in accordance to your proposal. The revision process has made the manuscript clearer and heightened the quality.*

Other suggestions:
Please describe the full names of all acronyms/abbreviations on their first appearance in the text of the manuscript.

*Response: Done. Thank you.*

Please make it clear when COVID-19 (the disease) or SARS-CoV-2 (the virus) should be used.

*Response: Done. Thank you.*

There are some typographical errors. Please review this.

*Response: Done. Thank you.*

**Competing Interests:** No competing interests were disclosed.
The authors indicate that the experiment program will be a multicomponent rehabilitation program with an intervention and a follow-up using programmed telemedicine sessions.

A key aspect of telemedicine is the closure of the patient-doctor loop and feedback. The authors of the summary report do not indicate if and what the feedback will be.

The abstract also states that "results are expected to be disseminated to the scientific community during and after the end of the study." However, the key to presenting the results is to complete the research and obtain the results, hence the question of how the authors will deliver the results without getting them.

The authors indicate that "COVID-19 infection causes various clinical manifestations in patients, including neurological manifestations, ranging from headache, dizziness, neuralgia, and neuropathy, to musculoskeletal symptoms and myalgia." However, the authors do not point to specific symptoms or how to distinguish them from pain syndromes unrelated to COVID-19.

The authors also propose that the study group should have a different study protocol which consists of "education, respiratory exercise, mobility, and stretching, giving them a place to provide feedback and re-evaluate patients mid-treatment." In this situation, will the group without distance assessment (I do not write telemedicine because it has not been clearly defined) also not have "education, respiratory exercise, mobility, and stretching, giving them a place to provide feedback and re-evaluate patients mid-treatment"? If not, the study groups cannot be compared.

The authors report, "Physical therapists involved in face-to-face treatment will not know which sample also has a telemedicine focus." This may suggest an attempt at randomization. So how is randomization going to work? How will patients be allocated to groups? If patients have different symptoms at different locations, how do the authors want to classify them as a homogeneous study group? A checklist?

The authors also want to compare subjects who are not informed whether they are taking painkillers or other drugs besides telling them whether they are taking medications. Taking painkillers may change the achievement of symptoms planned for collection. The introduction of additional exercises may also change the results significantly, making it impossible to compare the test group with the control group.

In the reviewer's opinion, the study protocol requires explicit declarations and ensures the comparability of the test group with the control group.

Regarding "variables will be measured by being able to predict a change in the primary measurement results between the first and second measurement." What information do the authors expect to gain from the items concerning:
Loss of family members due to COVID-19 (SARS-CoV-2): refers to the loss of family members in subjects due to COVID-19 disease, being classified as a qualitative dichotomous "yes/no" variable.

Chronicity refers to the number of years that the subjects in the sample have been suffering from symptoms so that it will be classified as a continuous quantitative variable.

Medication: refers to the number of drugs used to treat pain so that it will be classified as a continuous quantitative variable.

Is the question about family members supposed to relate to the mental state and mood disorders and the more difficult participation in rehabilitation associated with it? Will the question give information about the duration of the symptoms? Will the question about the number of drugs determine which groups of medicines affecting the study’s results are used by patients?

A final concern about the submission is how the authors explain the co-author’s involvement in the data curation activity in the absence of available data from this study.

Is the rationale for, and objectives of, the study clearly described?
Partly

Is the study design appropriate for the research question?
Partly

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Orthopedics, traumatology, sports medicine, spinal surgery, telemedicine, teleorthopaedics, telerehabilitation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
rehabilitation program with an intervention and a follow-up using programmed telemedicine sessions.

A key aspect of telemedicine is the closure of the patient-doctor loop and feedback. The authors of the summary report do not indicate if and what the feedback will be.

Response: We appreciate your comments with the intention of improving the manuscript. In "Study design", we add "A once a week telemedicine session will be carried out with the case group only before the face-to-face sessions, consisting of education, respiratory exercise, mobility and stretching, giving them a place to provide feedback and re-evaluate patients mid-treatment (Figure 2) and will be aimed at assessing improvement and improving therapeutic adherence."

Thank you.

2. The abstract also states that "results are expected to be disseminated to the scientific community during and after the end of the study." However, the key to presenting the results is to complete the research and obtain the results, hence the question of how the authors will deliver the results without getting them.

Response: The sentence has been changed to "the results are expected to be disseminated to the scientific community after the end of the study." Thank you.

3. The authors indicate that "COVID-19 infection causes various clinical manifestations in patients, including neurological manifestations, ranging from headache, dizziness, neuralgia, and neuropathy, to musculoskeletal symptoms and myalgia." However, the authors do not point to specific symptoms or how to distinguish them from pain syndromes unrelated to COVID-19.

Response: Thank you very much for your comment. We have added the following sentence "COVID-19 infection causes various clinical manifestations in patients, including neurological manifestations, ranging from headache, dizziness, neuralgia, and neuropathy, to musculoskeletal symptoms and myalgia. Some of the most commonly reported symptoms of COVID-19 include fatigue, cough, fever, ageusia (loss of taste), anosmia (loss of smell), and dyspnea (shortness of breath). In addition to these symptoms, some people may experience a headache, chest pain, or palpitations."

4. The authors also propose that the study group should have a different study protocol which consists of "education, respiratory exercise, mobility, and stretching, giving them a place to provide feedback and re-evaluate patients mid-treatment." In this situation, will the group without distance assessment (I do not write telemedicine because it has not been clearly defined) also not have "education, respiratory exercise, mobility, and stretching, giving them a place to provide feedback and re-evaluate patients mid-treatment"? If not, the study groups cannot be compared.

Response: Thank you very much for your comment. We have added the following sentence “The same protocol will be performed once a week in the control group prior to the face-to-face sessions so that comparisons can be made between the two groups”.

5. The authors report, “Physical therapists involved in face-to-face treatment will not know
which sample also has a telemedicine focus." This may suggest an attempt at randomization. So how is randomization going to work? How will patients be allocated to groups? If patients have different symptoms at different locations, how do the authors want to classify them as a homogeneous study group? A checklist?.

Response: Thank you very much for your comment. We have removed that sentence/statement, since we include the same telerehabilitation protocol in face-to-face sessions, we cannot ensure the blinding of the physiotherapists who perform the intervention by the multicomponent rehabilitation program.

6. The authors also want to compare subjects who are not informed whether they are taking painkillers or other drugs besides telling them whether they are taking medications. Taking painkillers may change the achievement of symptoms planned for collection. The introduction of additional exercises may also change the results significantly, making it impossible to compare the test group with the control group.

Response: Answer: Thank you very much for your comment. Since the patients belong to the referral hospital, we have the record of their medical history, which contains all their information regarding the consumption of drugs. These will be taken into account, especially those that could influence the results. If the patients meet the inclusion and exclusion criteria, the pertinent statistical analyses will be carried out, since we want to verify whether drugs consumption decreases after the intervention, taking as a reference another study in which we found results in this respect: Sánchez Romero EA, Fernández-Carnero J, Calvo-Lobo C, Ochoa Sáez V, Burgos Caballero V, Pecos-Martín D. Is a Combination of Exercise and Dry Needling Effective for Knee OA? Pain Med. 2020 Feb 1;21(2):349-363.

7. In the reviewer's opinion, the study protocol requires explicit declarations and ensures the comparability of the test group with the control group.

Response: Thank you for your comment. We have added the following sentence "The case group and the control group will have identical or similar characteristics, except that the cases will be treated with the multicomponent rehabilitation program plus telemedicine, and the control group with the multicomponent rehabilitation program and the same protocol in face-to-face sessions".

8. Regarding "variables will be measured by being able to predict a change in the primary measurement results between the first and second measurement." What information do the authors expect to gain from the items concerning: "Loss of family members due to COVID-19 (SARS-Cov-2): refers to the loss of family members in subjects due to COVID-19 disease, being classified as a qualitative dichotomous "yes/no" variable."

Response: We appreciate your comment. In our study, the aforementioned variables are modulating variables. We intend to collect this information and check for a possible influence on the results. Thank you.

9. "Chronicity refers to the number of years that the subjects in the sample have been
suffering from symptoms so that it will be classified as a continuous quantitative variable."

Response: We have modified the text to “Chronicity refers to the number of months that the subjects in the sample have been suffering from symptoms so that it will be classified as a continuous quantitative variable.” Thank you

10. "Medication: refers to the number of drugs used to treat pain so that it will be classified as a continuous quantitative variable."
Is the question about family members supposed to relate to the mental state and mood disorders and the more difficult participation in rehabilitation associated with it? Will the question give information about the duration of the symptoms? Will the question about the number of drugs determine which groups of medicines affecting the study’s results are used by patients?

Response: We welcome your comments. We appreciate your comment. In our study, the aforementioned variables are modulating variables. We intend to collect this information and check for a possible influence on the results. We have modified the variables section from “Predictive variables” to “Modulating variables”. Thank you.

11. A final concern about the submission is how the authors explain the co-author’s involvement in the data curation activity in the absence of available data from this study.

Response: Thank you very much for your comment. We have removed this part from the related section.

Competing Interests: No competing interests were disclosed.