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Study design

Neuromuscular Electrical Stimulation (NMES) as an Add-on Therapy for the Improvement of Dyspnea in Patients with Post-Covid Syndrome: a Protocol for a Phase II Randomized, Non-Pharmacological Intervention-Controlled, Double-Blind Study

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ABSTRACT:

Introduction: To date, 501 million people have been infected with SARS-CoV-2 and the incidence of COVID-19 is still increasing as new variants develop. Beyond the well-known short-term consequences of morbimortality of the COVID-19 disease, multiple long-term sequelae have been identified, which are referred to as Post COVID Syndrome (PCS). Dyspnea beyond three weeks from infection is the most common long-term symptom, and physical therapy is the standard care for those patients. Neuromuscular Electrical Stimulation (NMES) has been previously used to improve muscle weakness in different pulmonary diseases with promising results. Therefore, given the expected burden of disease, additional tools that seek to optimize patient care, which are easy to use and cost-effective, are a promising approach to PCS recovery. Objective**:** To compare the efficacy of NMES plus physical therapy against sham procedure and physical therapy in improving dyspnea among patients who developed PCS.

Methods: This trial will be a multicentric randomized sham-controlled, double-blinded parallel phase 2 superiority trial. Patients admitted to the hospital with moderate to severe COVID-19, who develop PCS, will be allocated to intervention and sham groups in a 1:1 ratio. They will be assessed for dyspnea through the 6-minute walk test (6MWT) for three months.

Conclusion: To our knowledge, no previous published literature tested the same intervention array as this study. Thus, the study assesses the possible impact of the proposed intervention to improve dyspnea among patients with PCS.

Keywords: COVID-19, Post-COVID Syndrome, Post-acute COVID, Long COVID, Neuromuscular Electrical Stimulation, Dyspnea.

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Introduction

The Coronavirus-2 (SARS-CoV-2) or Coronavirus disease 2019 (COVID-19) outbreak was considered a Global Pandemic by the World Health Organization (WHO) by March 2020 (WHO, 2020). Currently, 501 million people worldwide have been infected and almost 6.2 million died due to severe acute respiratory syndrome Coronavirus 2 (WHO, 2020).

Beyond the short-term consequences of the morbimortality of the virus, long-term sequelae were also identified. Post-COVID Syndrome (PCS), also known as post-acute COVID or long COVID, is an emerging health challenge. PCS is defined as the permanence or development of symptoms four weeks or more after the onset of infection (Centers for Disease Control and Prevention [CDC], 2021) and it has been seen to affect up to 80% of COVID-19 patients, based on global data (Cabrera Martimbianco et al., 2021). PCS has been associated with long-term multiorgan impairments involving the respiratory, cardiac, neurological, digestive, and musculoskeletal systems (Burgess et al., 2021). A recent meta-analysis reported that PCS usually manifests as fatigue, shortness of breath, cough, anxiety, depression, and psychological distress. Dyspnea is the most common long-term residual phenomenon (Morin et al., 2021; Huang et al., 2020).

Dyspnea can be defined as a "subjective experience of breathing discomfort that consists of qualitatively distinct sensation that varies in intensity" (American Thoracic Society [ATS], 1999). The mechanism for developing dyspnea in patients with PCS is not well understood. However, it is hypothesized that organ damage, sepsis complications, muscle deconditioning, dysautonomia, and exercise hyperventilation are potential causes (CDC, 2021).

PCS management and prevention pose a severe public health challenge, especially as new COVID variants arise. To date, physical therapy is the standard care for patients with PCS, and no conclusive recommendations have been provided to support other non-pharmacological interventions for this condition. In addition, it has been hypothesized that Neuromuscular Electrical Stimulation (NMES) is a safe and effective non-pharmacological intervention for improving muscle weakness in different pulmonary diseases (Minetto et al., 2021).

NMES consists of the application of small intermittent electrical stimuli to the skin above skeletal muscles to generate involuntary muscle contractions by excitation of motor nerves. Its benefits for PCS patients are due to the maintenance of blood flow, reduction of edema (Burgess et al., 2021), strengthening of the muscles, and prevention of muscle atrophy caused by extended hospital bed rest, among other complications (Burgess et al., 2021). Systematic reviews have shown that NMES added to standard care is more effective than standard care alone in preventing Intensive Care Unit (ICU)-acquired muscular weakness (Maffiuletti et al., 2013) and in improving quality of life (QoL) in individuals with chronic respiratory illness (Valenza et al., 2017).

Of note, knowledge around this new condition is still evolving, and interventions to reduce PCS impact are limited and inconclusive. Hence, we seek to optimize patient care with cost-effective, easy-to-use tools.

Thus, the present study's primary objective is to compare the efficacy of NMES plus physical therapy against sham procedure plus physical therapy in improving dyspnea, measured by the 6-minute walk test (6MWT). During three months, the focus will be on patients admitted to the hospital with moderate to severe COVID-19 disease and who developed PCS. The secondary objective is to compare the efficacy between the groups measured by additional pulmonary function tests (PFT).

Materials and Methods

Trial Design

This will be a multicentric, randomized, sham-controlled, double-blinded, parallel-group, phase 2 superiority study. Allocation will be in a 1:1 ratio between intervention and sham groups.

Study Setting

Due to the increased vaccination rate, hospitalization incidence due to SARS-CoV-2 infection is expected to decrease. Therefore, to achieve our expected sample size (N =444), we would need ten tertiary centers treating COVID-19 across the United States. These centers must have facilities for physical therapy and comply with US Food and Drug Administration (FDA, 1999) approved NMES technology. Sites selection will be based on the patient's volume, structure, and geographical distribution, along with the staff experience in treating disease, usage of NMES, and ability to comply with Good Clinical Practices.

Randomization

Randomization sequence generation

The randomization sequence will be generated through a web-based system, allocating in a 1:1 ratio to either intervention or control group using block randomization stratified by site.

Randomization - Allocation concealment

Allocation sequences will be implemented using computer-generated codes, which will be released once the trial ends. The allocation sequence will be blinded to the health care provider but not to the physical therapist (PT).

Randomization - Implementation

Blinded site staff will enter patients' information into the database and the randomization process will begin. The system will send each randomization number to a healthcare provider who will provide the treatment, not being responsible for assessing the outcomes. A blinded trial coordinator will be informed of participant enrollment and will assign the itinerary for PT/nurses' visits.

Blinding

Trial participants, outcome assessors, data managers, and biostatisticians will be blinded. The PT responsible for administering both NMES and sham NMES will be unblinded. Unblinded PT will apply the electrodes to the participants, set up the NMES device for the required current intensity (intervention or control), cover the equipment screen with curtains, and leave the room. A blinded PT will then enter the room. During the electrical current application, the blinded staff will stay in the room in case of discomfort or need assistance. Both blinded and unblinded PTs will be trained to keep the study blinding.

Participants from both groups will be scheduled at different times of the day to avoid unblinding. Blinding success will be assessed one month after the trial's onset through Bang's index (Bang et al., 2004).

Emergency unblinding

Trial subjects, PTs, and evaluating physicians will be sent an email regarding the contact details for emergency unblinding. In case of unblinding, the Institutional Review Board (IRB) will be notified and the unblinding will be documented.

Emergency unblinding will occur in case of the development of any critical and/or unstable medical condition with potential contraindication for a 6MWT and/or NMES, as determined by the evaluating physician.

Inclusion Criteria

Age >18 years (1); confirmed initial SARS-CoV-2 infection with a positive Reverse Transcription - Polymerase Chain Reaction test (2); patients with previous moderate COVID-19 disease (defined as patients suffering from fever, respiratory tract symptoms and imaging suggesting pneumonia) and those with previous severe COVID-19 disease (Shortness of Breath, Respiration Rate >30, O2 saturation <93% at rest, Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration <300 mmHg) (Shu et al., 2021), who developed Post COVID dyspnea (new, or recurring symptoms between 4 to 8 weeks after the initial infection, as per CDC definition) (CDC, 2021) (3).

Exclusion Criteria

Patients with previous mild (mild symptoms treated in an outpatient) and critical COVID-19 infection (defined as those with respiratory failure and the need for mechanical ventilation, shock, other organ failure and need for ICU monitoring and treatment) (Shu et al., 2021) (1); patients with a history of non-reversible pre-existing respiratory conditions (i.e. pulmonary fibrosis and Chronic Obstructive Pulmonary Disease (COPD) (2); patients with contraindications to NMES (uncontrolled arrhythmias, unstable angina, recent myocardial infarction (MI), electrical devices such as pacemakers, intracranial clips and total knee/hip replacement, lower limb malignancy, deep vein thrombosis and pregnancy (Bourjeily-Habr et al., 2002) (3); patients with contraindications to the 6MWT (acute MI, acute Pulmonary Embolism, decompensated Heart Failure, acute myocarditis/pericarditis, disorders that may affect exercise performance like Renal Failure and thyrotoxicosis, severe hypoxia at rest, mental impairment and patients with amputations or physical

disability that prevents them from ambulating) (ATS, 2002) (4); patients with Body Mass Index ≥ 35 (5); patients already enrolled in physical therapy (6).

Recruitment Strategy

Patients who meet the initial inclusion criteria will be identified during their hospital admission or post-admission follow-up visit.1

Patients will initially be screened via a telephone call four weeks or more after their initial diagnosis of SARS-CoV-2 infection. We will use the modified Medical Research Council (mMRC) dyspnea scale score, a validated tool to assess dyspnea in patients with chronic pulmonary disease (Mahler & Wells, 1988). Patients will be excluded if unreachable after three attempts.

Patients with a positive mMRC dyspnea scale score will be considered for inclusion in the study. After obtaining verbal consent, patients will be scheduled for an initial visit at an outpatient clinic and undergo a comprehensive medical evaluation to confirm eligibility. Patients will be screened for cardiac symptoms prior to the beginning of the exercise program.

Once the inclusion and exclusion criteria are met, the procedures and risks will be explained to the subjects followed by a consent documentation signature.

Baseline testing will be obtained, including Chest X-Ray, 6MWT, PFT, and initial physical therapy assessment.

Adherence

Consistent with previous similar research (Burgess et al., 2021) and to guarantee participants' adherence, a PT involved in the study will provide information to the patient about the NMES device. The PT administering the NMES will also set the device amplitude to a comfortable and pain-free level.

To enhance intervention adherence, text message reminders will be sent the day before the session (specifying the session's place, date, and time). Furthermore, participants will be provided with a phone number to contact the PT if additional questions arise. All communications with participants will be standardized to maintain participant masking.

The nurse or PT will contact participants who miss one session by phone. Reasons for not attending will be collected, and the visit will be rescheduled.

To enhance data validity, adherence will be assessed by reviewing the patient logbook containing information regarding the visits. Moreover, during the intervention phase, patients will be questioned about the reasons for non-adherence, including the possibility of NMES dislike, dizziness, discomfort, and pain, and responses will be documented.

Timeline

See Figure 1.

Interventions

30-minute NMES sessions will be held for three months, three times a week, after participants have completed 30-minute physical therapy sessions (Bourjeily-Habr et al., 2002). A PT will supervise the sessions of both modalities. NMES devices in the selected facilities are portable, user-friendly, with dual-channel stimulators, and comply with FDA regulations (FDA, 1999).

The intervention group will receive conventional physical therapy offered by the unit's PT, including stretching, straightening, and gait training according to the patient's needs. After the 30-minute exercise session, NMES will be applied in the central aspect of the quadriceps muscles using self-adhesive, pre-gelled 5x5cm (2x2") square electrodes (Burgess et al., 2021). The intensity will be adjusted to sensory tolerance with a biphasic pulse of 50 Hz and a pulse duration of 400 ms of synchronous stimulation for 15 minutes, followed by a 15 minutes break to avoid muscular fatigue. After that, another 15 minutes of NMES will take place, completing 30 minutes of NMES.

Control group: Patients in this group will also receive conventional physical therapy. After completing 30 minutes of exercise, sham NMES will be applied in the same muscle distribution for 15 minutes, followed by a 15 minutes break, after which NMES will be applied again, completing 30 minutes of sham NMES. Sham NMES has the same appearance as NMES in the intervention group, the only significant difference between groups being the device's setting. Current stimulation will be set at 10mA, a frequency of 10 Hz, and a pulse width of 350 μs with possible sensation but no visible muscle contraction (Burgess et al., 2021).

Modification/discontinuation

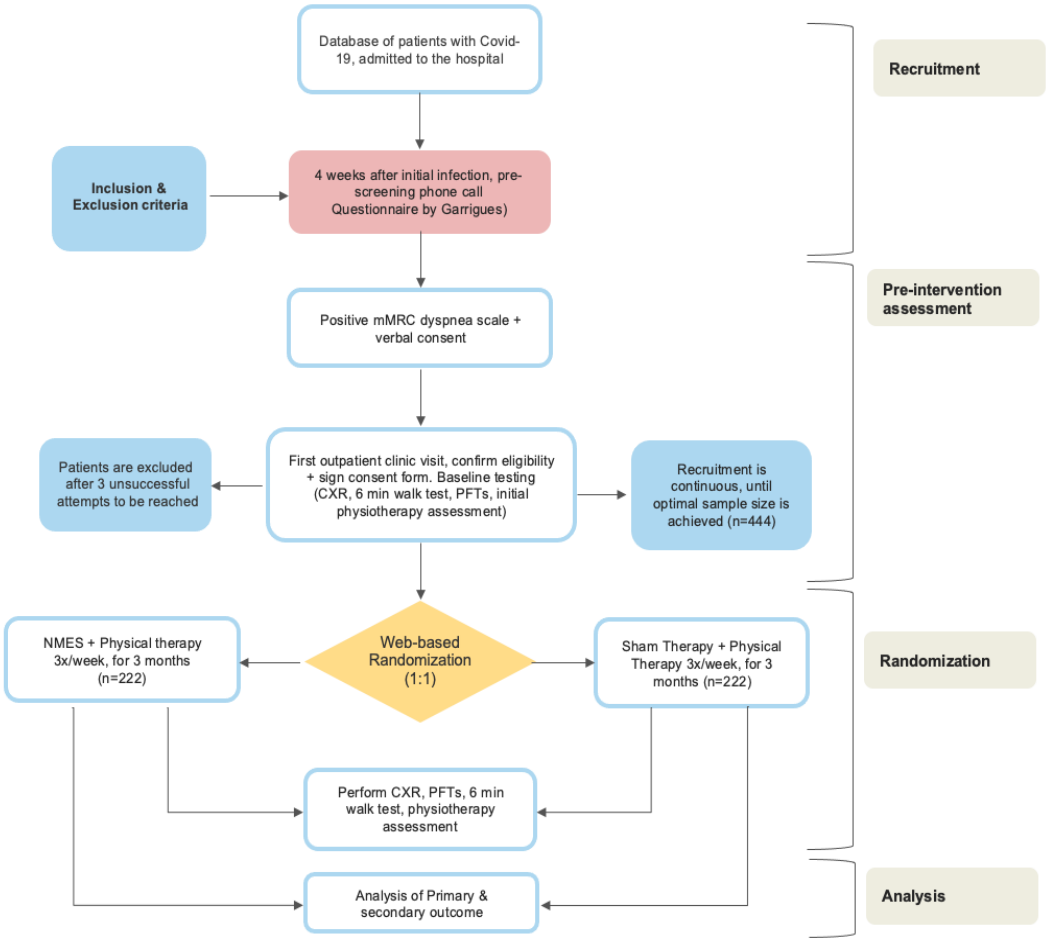

Figure 1. Strategic planning timeline

Developing sensitivity or skin irritation with the self-adhesive electrodes is a reason to modify them into carbon rubber electrodes.

The possibility of discontinuing treatment will be considered in case of an electrical surge or shock due to equipment malfunction (1); persistence of skin irritation after electrode changing (2); symptoms worsen after starting NMES (3); participants missing or unable to complete more than three visits (4).

Outcomes

The primary outcome will be the difference in the distance covered in 6MWT from baseline to 3 months between intervention and control groups.

Since the PFT would represent a composite of exams, this study opted for a functional test (6MWT) as the primary outcome to ensure a more straightforward interpretation of the results, as the composite outcome would add complexity to the statistical analysis. The 6MWT is a valid, simple, and widely used tool for physical functional capacity in patients experiencing respiratory disorders, being regulated by ATS (2002) guidelines. Moreover, the distance measured in 6MWT provides a more objective result, decreasing the chance of bias in subjective measurements. Thus, the PFT will be considered a secondary outcome.

The secondary outcomes are (1) dyspnea (measured by the modified Borg scale), (2) FEV1, (3) FVC, (4) FEV1/FVC ratio (FEV1%), (5) DLCO and (6) SpO2 during 6MWT. Based on those secondary outcomes, the study will also measure the proportion of participants presenting impairments in PFTs. To make results more comparable, given the yet limited research on PCS, the mentioned tests were chosen consistent with other published research.

All outcomes will be measured during the baseline visit and at the visit after three months of intervention. All tests will be performed before the 6MWT, except oxygen saturation, which will be measured during the 6MWT (ATS, 2002). The modified Borg scale will be measured before and after the 6MWT (Borg, 1998).

Data Management

Data Monitoring

All materials collected are for research purposes only. Data will be kept strictly confidential using

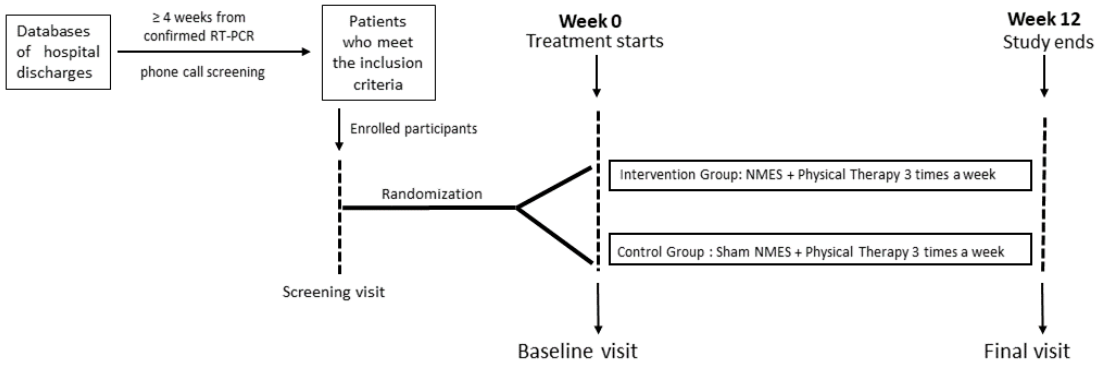

Figure 2. Timeline of outcome measurements.

subject identification codes and imported into a Stata dataset.

Data will be stored on a secure, password- and firewall-protected server maintained by our study group. Data will only be accessed by authorized study personnel (data analysts, statisticians, and outcome assessors) using encrypted, secure internet connections. The paper questionnaires will be retained for 3 years after the end of the study.

An ad-hoc independent Data and Safety Monitoring Committee (DSMC) composed of five professionals with different expertise (biostatisticians, clinical practitioners, and researchers with advanced clinical trials competence) will be established. Experts will not be related to the research in any other way, avoiding conflict of interest.

Interim Analysis

Since our study will be conducted in a population at elevated risk of severe health outcomes, an interim analysis will be conducted when 50% of patients have completed the follow-up. A statistician, blinded to treatment allocation, will conduct the analysis and report to the independent DSMC, thus having unblinded access to all data. The primary outcome will be analyzed by the Pocock approach (Togo & Iwasaki, 2013). The study will be stopped due to operational futility (using symmetric stopping boundaries at $P < 0.029$).

Based on interim analyses results, the DSMC will contact the Trial Steering Committee to terminate the study if: NMES proves, according to the following interim analysis plan, to be different beyond doubt from the standard treatment for all or some types of participants (1); any important safety issue arises that may prompt the urge to terminate the study (2);

Sample Size Calculation

The sample size was estimated considering the effect size (distance improvement in 6MWT) of the existing literature. A difference of 26 meters was considered clinically significant (Puhan et al., 2011). Although pathologies with pulmonary involvement differ from those with a post-COVID syndrome, these studies provide similar rationale upon pulmonary tests, making their use for the sample size calculation in this study plausible.

Seven studies were found in the literature that performed 6MWT for COVID-19 patients and presented results as continuous quantitative variables (Appendix A); the mean distance was 514 meters with a Standard Deviation (SD) equal to 87 (Strumiliene et al., 2021; Salles-Rojas et al., 2021; Madrid-Mejía et al., 2021; Huang et al., 2020; Morin et al., 2021; Huang et al., 2021; Shah et al., 2020).

The dropout rate calculation was based on studies evaluating NMES and 6MWT simultaneously (Appendix B). Attrition rates were relatively high, ranging from 0% (Valenza et al., 2018) to 30% (Bonnevie et al., 2018). For this study, a dropout rate of 20% was considered based on the mentioned studies and the proposed retention strategies.

To detect a difference of 26 meters between the groups with 80% power and 0.05 significance level (two-tailed) while assuming equal variances, 177 participants per group will be required. Considering a 20% withdrawal rate, we plan to recruit 444 participants.

Statistical analysis for primary and secondary outcomes

Continuous data will be expressed as mean and SD or median and interquartile range, according to normality. Normally distributed continuous variables will be compared by linear regression, adjusted by the site. To compare categorical data, the results will be analyzed by logistic regression adjusted by site. Subgroup analysis will be carried out according to COVID-19 disease severity at patients' enrollment.

The intervention arm (NMES + physical therapy) will be compared against the control arm (sham NMES + physical therapy) for the primary analysis, which is defined as the difference in the distance

achieved in 6MWT from baseline after three months of intervention between groups. Being a parametric continuous variable, it will be analyzed by an unpaired t-test. For secondary outcomes, variables will vary according to the measure. The variables and the statistical methods of each are described in **Table 1**.

Given the potential difference in patient outcomes, a subgroup analysis will be carried out according to the severity of COVID-19 disease prior to the development of Post COVID dyspnea in each subject.

All analyses are based on the intention-to-treat population. All calculations will be performed in STATA 17.1 version.

Variable/Outcome	Outcome Measure	Type of variable	Methods of Analysis
*Measured at Baseline Visit (Week 0) and 3-month Visit (Week 12)			
1) Primary			
Functional test: distance in 6MWT after 3 months	Difference of distance in meters	Continuous	Linear regression
2) Secondary			
Subjective feeling of dyspnea	Modified Borg Scale rating (continuous)	Continuous	Linear regression
Pulmonary function test	Volume at Forced expiratory volume at the first second (FEV1) in liter		
	Volume at Forced Vital Capacity (FVC) in liter (continuous)		
	FEV1/FVC ratio (FEV1%)		
	% in diffusion capacity of the lungs for carbon monoxide (DLCO)		
Functional test	% of oxygen saturation (SpO2) during 6MWT		
Impairment in pulmonary function test	Proportion of participants who achieve DLCO <80%	Categorical	Logistic regression
	Proportion of participants who achieve FEV < 80%		
	Proportion of participants who achieve FVC <80%		
	Proportion of participants who achieve FEV1% <70%		

Table 1. Variables, Measures and Methods of Analysis.

Missing Data

Complete-case analysis and multiple imputations will be used to evaluate missing data. Given the expected high dropout rate (up to 20%), the validity of the results will be assessed by a sensitivity analysis.

Discussion

This research proposal hypothesizes that NMES could work as an add-on therapy to rehabilitate patients who experience dyspnea due to PCS, proved by an improvement in the 6MWT. The recovery process of patients who develop PCS is often complex and challenging. Among the non-pharmacological treatments available for the early rehabilitation of patients, NMES has been considered a promising approach for improving QoL, pulmonary function, and ICU-acquired muscular weakness in individuals with chronic respiratory illness (Maffiuletti et al., 2013). Furthermore, it helps prevent muscle atrophy, improve dyspnea, muscle strength, and function, maintain blood flow, and reduce edema (Burgess et al., 2021).

In previous RCTs, NMES has shown to be a valuable, straightforward, and non-invasive adjunct therapy to pulmonary rehabilitation for COPD patients (Bourjeily-Habr et al., 2002). It has also been shown to improve physical and functional performance in patients with pneumonia (Minetto et al., 2021), and post-intensive care syndrome (Minetto et al., 2021). However, no conclusive recommendations have been provided to support NMES as a non-pharmacological intervention for patients with PCS.

As a phase two trial, our study presents some limitations. It has adopted narrow eligibility criteria and excluded patients with critical COVID-19; even though this increases the internal validity, it also limits the generalizability of the findings. Due to the lack of literature and the low number of ongoing trials on the topic, defining minimal clinically significant differences in the 6MWT for PCS was challenging. This can impact the sample size calculation of the trial. Physical therapy, the standard care for PCS, will not be standardized for the study since patients with PCS can present with different symptoms requiring individualized physical therapy. Nevertheless, we decide to blind participants, outcome assessors, data managers, and biostatisticians.

Despite the mentioned limitations, our study design and easy-measure outcomes make our study feasible. Besides, NMES is an established rehabilitation technique that enables easy incorporation into a patient's regular clinical care; its technical execution is simple and makes its replicability easy to achieve by PT. Additionally, there is no scientific evidence of adverse effects and the patient's cooperation is minimal; thus, it has a high adherence rate (Maffiuletti et al., 2013).

Our study has the potential to prove that a low-cost, innovative, non-pharmacological treatment can improve PCS dyspnea as an add-on to the standard of care. This can also aid in developing guidelines for the optimal management of this population and shed light on further investigation.

Trial Registration: A trial identifier and registry name will be provided once the project is submitted to the intended registry. To register the current prospective clinical study of health outcomes using an applicable device, the NIH's clinical trials dissemination policy will be followed as it relates to the federal regulation (FDAAA Section 801 as implemented by 42 CFR Part 11). The responsible party for trial registration submission is Group 14 members.

Ethical Conflicts: Researchers must ensure that this study is conducted according to the United States and international standards of good clinical practice, applicable government regulations, and institutional research policies and procedures. Prior to conducting this research, this protocol as well as any amendments must be approved by the applicable IRB board. Overall, the potential risks associated with participation in the current study are low, and no subjects will be asked to perform any tasks that can result in physical harm.

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Conflicts of Interest: The authors have no financial or personal conflicts of interest related to this protocol. All authors approved the final version of this manuscript.

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