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ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COVID-19 (COVIDIMT): PROTOCOL FOR RANDOMIZED CONTROLLED DOUBLE-BLIND TRIAL.

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Complete List of Authors:
Maldaner, Vinicius ; UniEVANGELICA University Center of Anapolis Medical Course,
Coutinho, Jean; UniEVANGELICA Centro Universitario de Anapolis, 1- Human Movement and Rehabilitation Program,
Santana, Alfredo; Hospital Regional da Asa Norte, Pulmonolgy
Cipriano, Graziella; University of Brasilia, 3- Rehabilitation Sciences and Health and Technologies in Health Sciences Program
Oliveira, Miriã; UniEVANGELICA Centro Universitario de Anapolis, Human Movement and Rehabilitation Program
Carrijo, Marilúcia de Morais; UniEVANGELICA Centro Universitario de Anapolis, Human Movement and Rehabilitation Program
Lino, Maria Eduarda; UniEVANGELICA Centro Universitario de Anapolis, Human Movement and Rehabilitation Program
Cahalin, Lawrence; University of Miami School of Medicine, Physical Therapy
Lima, Alexandra; Hospital Regional da Asa Norte
Borges, Robson; University of Brasilia, 3- Rehabilitation Sciences and Health and Technologies in Health Sciences Program
santos, Dante; UniEVANGELICA Centro Universitario de Anapolis, Human Movement and Rehabilitation Program
Silva , Iransé ; UniEVANGELICA Centro Universitario de Anapolis, Physical Education
Oliveira, Luis Vicente; UniEVANGELICA Centro Universitario de Anapolis, Human Movement and Rehabilitation Program
Cipriano, Gerson; Universidade de Brasília, Faculdade de Ceilândia

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ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COVID-19 (COVIDIMT): PROTOCOL FOR RANDOMIZED CONTROLLED DOUBLE-BLIND TRIAL.

Short Title: Inspiratory muscle training in COVID-19 patients

Vinicius Maldaner[1,2]; Jean Carlos Coutinho[1], Alfredo Nicodemos da Cruz Santana[2]; Graziella F. B. Cipriano[3], Miriã Cândida Oliveira[1], Marilúcia de Morais Carrijo[1], Maria Eduarda Moreira Lino[1], Lawrence P. Cahalin[4], Alexandra G.B Lima[3]; Robson Borges[3], Dante Brasil Santos[1]; Iransé Oliveira-Silva[1]; Luis Vicente Franco de Oliveira[1], Gerson Cipriano Jr[3];

Affiliations:

1- Human Movement and Rehabilitation Program, University Center of Anápolis UniEvangelica, Anápolis, Goiás, Brazil.
2- Hospital Regional da Asa Norte, HRAN, Brasília – Brazil.
3- Rehabilitation Sciences and Health and Technologies in Health Sciences Program, University of Brasilia, Brasilia, Federal District, Brazil.
4- Department of Physical Therapy, University of Miami Miller School of Medicine, Coral Gables, Florida, USA

Vinicius Maldaner – Conceived and designed the experiment

Jean Carlos Coutinho: - Investigation and Resources

Alfredo Nicodemos C. Santana: Original draft preparation.

Graziella FB Cipriano – Original Draft preparation

Miriã Cândida Oliveira – Pulmonary Rehabiliation Program

Marilúcia de Morais Carrijo – Pulmonary Rehabiliation Program

Maria Eduarda Moreira Lino – Pulmonary Rehabiliation Program

Lawrence Cahalin: Conceived and designed the experiment

Alexandra CGB Lima: Investigation and Resources

Robson Borges- Pulmonary Rehabiliation Program

Dante Brasil Santos – Investigation and Resources

Iransé Oliveira-Silva – Original Draft Preparation

Gerson Cipriano Jr - Conceived and designed the experiment

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All authors have no conflicts to disclosure.

Corresponding Author:

Vinicius Maldaner

SQN 305 Bloco D apto 102 – Asa Norte – Brasília DF Brazil

PO BOX 70737-040

Phone Number: + 55 61 33688536

Email: viniciusmaldaner@gmail.com

WORD COUNT: 2854

ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COVID-19 (COVIDIMT): PROTOCOL FOR RANDOMIZED CONTROLLED DOUBLE-BLIND TRIAL.

ABSTRACT

Introduction: A significant number of patients with COVID-19 will have dyspnea, anxiety, depression, pain, fatigue, and physical impairment symptoms, which may reveal the need for a multidisciplinary rehabilitation approach, especially for those patients with advanced age, obesity, comorbidities, and organ failure. Pulmonary rehabilitation (PR) involves exercise training, inspiratory muscle training (IMT), psychosocial counseling, and education, which has improved pulmonary function, 6-minute walk test, and quality of life in COVID-19 patients. The addiction of IMT in PR programs is still uncertain. This study aims to determine if supervised-IMT plus PR is more effective than PR alone to improve dyspnea, health-related quality of life, and exercise capacity in symptomatic post-COVID-19 patients.

Method and Analysis: This parallel-group, assessor-blinded randomized controlled trial, powered for superiority, aims to assess exercise capacity, dyspnea and health-related quality of life as primary outcomes. One hundred twenty participants are being recruited at three PR centers in Brazil. Following baseline testing, participants are randomized

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using concealed allocation, to receive either: a) standard PR with sham IMT or b) standard PR plus IMT. The main analyses will be intended to treat and assess the impact of compliance on outcomes using a complier average causal effect analysis.

Ethics and Dissemination: This trial was approved by the Conselho Nacional de Saúde (CONEP) Ethics Committee and received approval 07/10/2020 (Document number 4324069). Findings will be disseminated through publication in peer-reviewed journals and conference presentations.

Trial registration: This trial was prospectively registered on the Clinical Trials Registry NCT04595097

Key words: coronavirus, rehabilitation, breathing exercises.

Strengths and Limitations of this study

- Evaluation of economic efficiency in addition to clinical effectiveness.
- The first fully powered study comparing inspiratory muscle training plus pulmonary rehabilitation with sham inspiratory muscle training plus pulmonary rehabilitation in post-COVID 19 patients.
- Full therapist blinding not possible.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has rapidly evolved into a global health emergency. The disease progression varies widely, including hypoxia, dyspnea, and respiratory failure (1). A significant number of patients with COVID-19 will have dyspnea, anxiety, depression, pain, fatigue, and physical impairment symptoms, which may be related to Post Intensive Care Syndrome (PICS) (2). The above symptoms and limitations of the PICS may persist for years, such as non-COVID-19 acute respiratory distress syndrome patients (3). Persistent and late-onset symptoms described after

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COVID-19 include dyspnea and fatigue, which may persist for more than 120 days after symptom onset (4). Recent literature examining the consequences of infectious diseases like severe acute respiratory syndrome (SARS) and COVID-19 has identified respiratory muscle weakness that persists for a long time after the initial infection [11].

Further research is needed to identify if particular treatment strategies may reduce the duration of symptoms after COVID-19. Recent SARS-CoV-2 experience has revealed the need for a multidisciplinary rehabilitation approach, especially for those patients with advanced age, obesity, comorbidities, and organ failure (5).

An International European Respiratory Society (ERS) and American Thoracic Society (ATS) Task Force suggests that COVID-19 survivors with a need for rehabilitative interventions at 6-8 weeks following hospital discharge should receive a comprehensive pulmonary rehabilitation (PR) program (6). Although most studies have evaluated the effects of PR in patients with Chronic Pulmonary Obstructive Disease (COPD), there is evidence that it is a treatment option for other pulmonary conditions such as idiopathic pulmonary fibrosis (IPF) and COVID-19 (7). PR has been advocated to provide comprehensive care, improve functional status, reduce symptoms, and decrease healthcare usage in patients with respiratory diseases (8). PR involves exercise training, psychosocial counseling, and education, and recently the ERS advocated that inspiratory muscle training (IMT) should be considered as an additional intervention in PR programs, especially in patients with inspiratory muscle weakness (10).

A recent study examining the PR effects in elderly patients with COVID-19 (11) significant improvements in pulmonary function, 6-minute walk test, and quality of life [9]. Additionally, a recent case report has also described a substantial effect from a PR, including the IMT method on respiratory muscle strength, besides the additional benefits on arterial blood gases and functional performance (12) on 17 patients; in a recent meta-analysis, authors also demonstrated positive results on dyspnea and health-related quality of life in IPF 362 patients, associating the IMT with aerobic exercise (13). Contrarily, Charusin et al. found that the addition of IMT in a general PR program did not translate

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into improvements in 6-minute walk distance, but the IMT program was unsupervised (14).

We believe that the benefits of IMT are linked to frequent monitoring and optimal progression of IMT sessions to ensure high-quality training sessions. Of note, few controlled clinical trials have investigated the addition of IMT in PR for patients with respiratory diseases. However, IMT combined with aerobic exercise training in patients with heart failure appears to be associated with significantly greater improvements in maximal inspiratory pressure (MIP) and quality of life with trends for greater maximal oxygen consumption and exercise duration than either IMT or aerobic exercise training alone (12).

In view of the above, this trial aims to determine if supervised-IMT plus PR is more effective than PR alone to improve dyspnea, health-related quality of life, and exercise capacity in symptomatic post-COVID-19 patients. We hypothesize that adjunctive supervised IMT will improve these patients and be cost-effective since it will be implemented in the PR programs. This protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT guidance) (15).

METHODS AND ANALYSIS

Study Design

This study's design is a pragmatic randomized, double-blind controlled trial with two parallel groups (arms), being conducted at three PR centers at Anápolis and Brasilia cities in Brazil. This protocol follows the SPIRIT Guidelines (15). The flowchart of the study protocol is demonstrated in **Figure 1.**

Patient and Public involvement

Patients and the public will be not directly involved in the design, recruitment to or conduct of this study. They will be involved in our plans to disseminate the study results

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to participants and relevant community groups by assisting in the choice of what information/results to share and in what format.

Participants

Eligible participants will be identified through screening after intensive care unit discharge. To be eligible, participants must be over 18 years of age with a confirmed COVID-19 diagnosis (16) that required hospitalization and either i) non-invasive respiratory support (CPAP, high-flow oxygen catheter, non-breathing oxygen mask, or ii) invasive mechanical ventilation within three months of study recruitment. Exclusion criteria will include pregnancy, dependence on others to perform activities of daily living during the month prior to the current ICU admission (gait aids are acceptable), documented cognitive impairment, proven or suspected spinal cord injury, or other neuromuscular diseases that will result in a permanent or prolonged weakness (not including ICU acquired weakness), severe neurological disease, death is deemed inevitable as a result of the current illness and either the patient or treating clinical or substitute decision-maker are not committed to full active treatment.

For enrolment into the study, informed consent will be sought from the person legally responsible for providing consent according to Brazil's Federal laws.

Randomization and allocation

Following informed consent and all baseline assessments, participants will be randomized at a 1:1 rate, according to the block randomization generated by the (https://www.sealedenvelope.com) to either the first intervention group (PR plus IMT) or the control group (PR plus sham IMT). An independent researcher of the trial will prepare the randomization schedule. Staff conducting outcome measurements will be blinded to allocation status.

Ethics and Dissemination

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The trial will be conducted in accordance with the Declaration of Helsinki and was approved by the Conselho Nacional de Saúde (CONEP) Ethics Committee and received approval 07/10/2020 (Document number 4324069). This trial was prospectively registered in the Clinical Trials Registry Platform on 20/10/2020 (NCT04595097). Recruitment commenced in February 2021.

Blinding

The patients and the assessors will be not explicitly informed about allocation. Staff conducting long-term outcome measurements will be blinded to allocation status.

Interventions

The intervention consists of a High-intensity IMT program, with a workload of 50% to 60% of the Maximal Inspiratory Pressure (MIP)/, including two sets of 30 breaths (60 breaths daily), with a 2-min interval in between work sets, 3 days per week, using a tapered flow-resistive loading (TFRL) device (14, 17) (POWERbreathe® KH2, HaB International Ltd, United Kingdon). The High-intensity IMT program will be associated with a PR program, following a previously published protocol [14, 16], for eight weeks.

Patients will be instructed and encouraged to perform 30 fast and forceful inspirations and be allowed to pause if necessary, though not exceeding 1 min (18). The maximal inspiratory pressure (MIP), maximal dynamic inspiratory pressure (S-Index) will be weekly updated to keep the training load to the highest tolerable load, 50 to 60% of the most recent MIP. The same trained physiotherapist will perform all respiratory muscle strength assessment.

The 10-points Modified Borg Dyspnea Scale will be utilized to assess dyspnea after each set of 30 breaths, and scores between 4 and 6 will also be used to adjust the IMT intensity. If the Borg score is less than 4 or higher than 6, the training load will be adjusted to higher

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or lower than 50% of the MIP, respectively (14, 17, 18). The control group's training workload will be set at 10% of the baseline MIP and will not be modified throughout the intervention period. Both groups will perform the same PR program. The IMT protocol will be performed daily after the PR program.

The PR staff will prescribe a tailored individualized PR program within pre-specified parameters recommended by pulmonary rehabilitation guidelines (19). The PR will be delivered thrice weekly, for 8 weeks (maximum 14 sessions [16 sessions total, including familiarization sessions]), of 30 to 50 min supervised exercise sessions, with progressive and individualized multi-modal exercises (including both aerobic, strength training, and functional fitness modalities). Adequate 5-min warm-up and a 5-min cool-down will be incorporated. According to previously determined ventilatory thresholds during a maximal cardiopulmonary exercise test, the intensity will be individually adjusted at the moderate domain and monitored by heart rate (HR) monitoring (10% range of the HR at first ventilatory threshold (1stVT)), rating of perceived exertion (4-6 in Borg scale), and oxygen saturation (above 90%), respectively.

Experienced physical therapists will perform familiarization sessions to optimize exercise prescription.

Primary Outcome measures

Cardiopulmonary exercise testing (CPX)

Subjects will underwent a maximum symptom-limited CPX (20), using cycle-ergometer ramp protocol (Corival, Lode, Netherlands) and ventilatory expired gas analysis cart (Quark CPET, Cosmed, Italy) following the recommendations of the European Respiratory Society for chronic lung diseases [19]. Volume and gas calibration will be performed before each test. Minute ventilation (VE), oxygen uptake (VO2), and carbon dioxide output (VCO2) will be acquired breath-by-breath and averaged over 10-second intervals. The ventilatory anaerobic threshold (VAT) will be determined by the V-slope

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method. Peak VO2 will be expressed as the highest 10-second averaged sample obtained during the final plateau if the patient reached it, or the last 20 seconds of testing, if not. The ventilatory efficiency (VE/VCO2 slope) will be calculated from a linear regression equation, from the start of the test to the exercise peak. The ventilatory reserve will be determined from FEV1 (calculated as 100-[VE/(FEV1x40)100]) (20). Circulatory power will be calculated from the VO2 and systolic blood pressure product at the peak, and ventilatory power from the quotient of peak systolic blood pressure and VE/VCO2 slope (21).

Health-related quality of life (HRQoL)

HRQoL will be assessed with the EQ-5D-5 L instrument, which is recognized as a validated generic HRQoL measure consisting of five dimensions, each one including five levels of response. Each answer combination will be converted into a health utility score (22).

EQ-5D-5 tool has good test-retest reliability, is simple to use, and gives a single preference-based index value for health status that can be used for cost-effectiveness analysis;

Dyspnea

Dyspnea will be assessed by the modified Medical Research Council Dyspnea Scale (mMRC). mMRC is a 0-4 scale used to classify dyspnea's impact on physical function in patients with respiratory limitations. On mMRC, 0 represents a person who suffers from dyspnea only with strenuous exercise, while 4 represents a person with a too breathless to leave the house or breathless when dressing or undressing (23).

Secondary Outcomes

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Anxiety and Depression

Anxiety and depression will be measured with the Hospital Anxiety and Depression Scale (HADS), a 14-item screening questionnaire from which an anxiety and depression subscale can be derived. Sub-score values > 5 points identify increased symptoms of anxiety or depression; a total score > 9 is considered indicative of psychological distress (24).

Fatigue

The fatigue will be captured using the Fatigue Severity Scale (FSS), a nine-item questionnaire validated to evaluate disabling fatigue. Each item is rated on a 7-point scale, from strongly disagree to strongly agree. A total score is derived from all nine questions; a higher score indicates a greater impact of fatigue on everyday activities (25).

Respiratory muscle strength

Respiratory muscle strength will be performed from residual volume using the technique proposed by Black and Hyatt to measure MIP and S-Index (26). Patients will be seated and motivate to perform a maximal voluntary exhalation effort at residual volume (RV), and then a verbal command was given to perform a maximal inspiratory effort, according to ATS standards (27). The patients will be oriented to perform 10 maneuvers, with 60-second rest intervals between the maneuvers, in order to reach the highest possible S-Index, but also seeking to avoid fatigue of the inspiratory muscles by using the maximum number recommended for similar evaluations (28).

Inspiratory muscle endurance will be assessed using a timed inspiratory endurance test (29), which consists of breathing against a submaximal load (40% of MIP) provided by the device (KH2, POWERbreathe®, UK) until task failure (Tlim in seconds).

Pulmonary Function Testing (PFT)

Spirometry was performed with a spirometer (Microlab 3.500; CareFusion, Yorba Linda, CA, USA). Three forced expiration maneuvers will be performed for validity and

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reproducibility purposes according to ATS/ERS criteria, with patients sitting, in a room with controlled temperature, ambient pressure, and relative humidity. The following variables will be analyzed: (a) forced vital capacity (FVC, L), (b) forced expiratory volume in the first second (FEV_1, L), and (3) FEV_1/FVC ratio (percentage). Obtained values will be recorded and compared to the predicted values for a Brazilian population (30).

Cost-utility (QALYs)

A cost-utility analysis using the EQ-5D-5L responses will be performed to generate quality-adjusted life years (QALYs), which will generate an incremental cost per QALY estimates credible intervals, cost-effectiveness acceptability curves, and value-of-information analysis (31).

Adverse Events

Adverse events will be defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention, and any such event does not necessarily have to have a causal relationship with this intervention. It is recognized that the patient population with a critical illness will experience several common signs and symptoms due to the severity of the underlying illness and the impact of standard therapies. These will not necessarily constitute an adverse event unless they are of concern or related to the study of the intervention in the investigator's clinical judgment. In all cases, the condition or disease underlying the symptom, sign, or laboratory value should be reported, e.g., tachycardia rather than chest palpitation. Following each intervention and outcome measure session, trial staff will be required to complete data entry forms indicating a severe or minor adverse event. In the case of serious adverse events, the study chief investigator will be notified immediately, participants will be managed appropriately, and the incident will be reported to the relevant hospital ethics committee. Adverse events will be collected from randomization to 48 hours post-cessation of our study protocol through phone calls.

Follow-up

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Outcomes will be assessed at 8 weeks and 16 weeks post-randomization. Figure 2 illustrates the schedule assessments of the participants. Patient-reported outcomes will also be collected at follow-up assessments. If any participants cannot attend the clinic, a postal questionnaire will be used to collect patient-reported outcomes.

Sample Size

The EQ-5D-5L has been used to estimate the sample size. To detect a minimally clinically important difference (MCID) between groups of 0.18 (32), assuming a standard deviation (SD) of the within-group differences in the questionnaire at the end of the intervention period of 0.06 in both groups with a statistical power of 80% and a risk for a type I error <5%, 65 patients will be included in each group, given an anticipated dropout rate of 20% based on previous pilot work or literature.

Data Analysis

Data will be summarized and reported in accordance with CONSORT guidelines for RCTs, using intention-to-treat analyses (33). The main analyses will be intended to treat and assess the impact of compliance on outcomes using a complier average causal effect analysis. Full compliance will be considered as attending at least 75% of the supervised exercise sessions. Also, the probabilities for achieving the desired effect size in each group will be presented using the magnitude-based inference approach. Pre-specified subgroup analyses will examine the interaction of treatment assignment. The analysis will be conducted using formal tests of interaction. The statistical methods will be further elaborated in a statistical analysis plan (SAP).

Trial Managing and Data Monitoring

The Trial Management Group, consisting of project staff and co-investigators involved in the day-to-day running of the trial, will meet monthly throughout the project. A Data Monitoring Committee consisting of independent experts with relevant clinical research and statistical experience will meet monthly to ensure data integrity, participant safety, and evaluation of any adverse events should they occur.

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Deidentified data and statistical code will be made available on request soon after each report of the data has been published. Different aspects of the data will be published separately, which will determine when those data are publicly available. A data-sharing agreement will require a commitment to using the data only for specified research purposes, to securing the data appropriately and to destroying the data after a nominated period.

DISCUSSION

Patients with chronic respiratory symptoms commonly develop deconditioning and weakness of the respiratory muscles, which is related to dyspnea and exercise intolerance in this population (34). Inspiratory muscle training (IMT) may reduce neural respiratory drive and subsequently improve abnormal breathing patterns, which may equalize the relationship between respiratory muscle demand and energy supply to the respiratory muscles. A recent meta-analysis showed that the inclusion of an IMT in a pulmonary program (PR) only improved respiratory muscle strength and that the presence of respiratory muscle weakness did not change the results (14). Langer et al. demonstrated that an 8-week home-based IMT program improved inspiratory muscle strength and dyspnea, reducing diaphragm activation at maximal exercise, which may be associated with an important physiologic response for the inspiratory muscles after IMT (35), which is compatible with the decrease of motor unit recruitment to generate a given force as a result of respiratory muscle hypertrophy.

While we acknowledge the value of traditional IMT protocols, which use mechanical loading devices, we believe that the IMT training with biofeedback provided by the POWERbreathe® KH2 device has the potential to provide added clinical benefits since it can modulate all aspects of muscular performance, including strength, power and work capacity. The real-time biofeedback likely encourages the generation of higher pressures throughout a full inspiration are features that differ from other IMT methods. Thus, IMT via the POWERbreathe® KH2 device can facilitate a more controlled breathing pattern with an improved gas exchange during and post-training.

Results from our study will provide several valuable information for many areas of clinical practice. Firstly, for clinicians and rehabilitation practitioners, providing information regarding exercise rehabilitation effects on chronic respiratory symptoms. Secondarily, health care providers, providing cost-effectiveness analysis of the PR and

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IMT methods in COVID-19 patients; and thirdly, patients following all viral types of pneumonia, providing potential benefits or harms effect, helping them better decide when is adequate to enroll into a physical activity and exercise programs.

Recruitment to the internal pilot will start in February 2021, and trial activities are expected to finish in August 2021.

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FIGURE LEGENDS

Figure 1: Flow chart

Figure 2: Template of recommended content for the schedule of enrolment, interventions, and assessments

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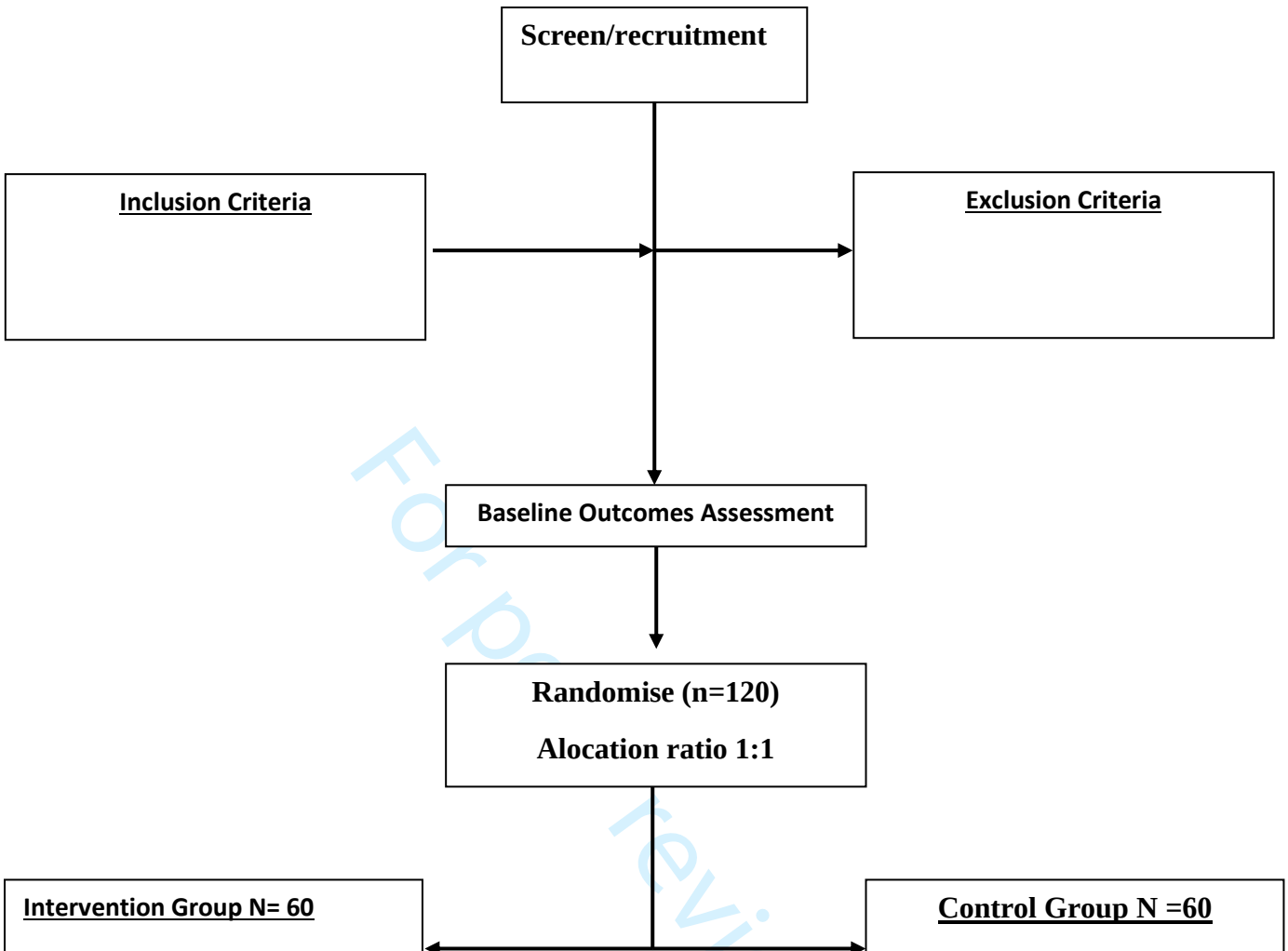

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Figure 2. **T**emplate of recommended content for the schedule of enrolment, interventions, and assessments.

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			
TIMEPOINT**	***-t_1***	**0**	***t_1*** *Baseline*	***t_2*** **8 Weeks**	***t3 16 weeks***	***t_x post analysis***
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
[IMT + Pulmonary Rehabilitation]			←	→		
[Sham IMT + Pulmonary Rehabilitation]			←	→		
ASSESSMENTS:						
[Clinical and Demographic Carachteristics]	X					
[Cardiopulmonary Exercise Testing]			X	X	X	
[mMRC]			X	X	X	
[EQ 5D 5L]			X	X	X	
HADS			X	X	X	
FSS			X	X	X	
Inspiratory Muscle Strength			X	X	X	
Inspiratory Muscle Endurance			X	X	X	
Cost-utility analysis						X

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

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

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

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

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

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BMJ Open

ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COVID-19 (COVIDIMT): PROTOCOL FOR RANDOMIZED CONTROLLED DOUBLE-BLIND TRIAL.

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Complete List of Authors:	Maldaner, Vinicius ; UniEVANGELICA University Center of Anapolis Medical Course, Coutinho, Jean; UniEVANGELICA Centro Universitario de Anapolis, 1- Human Movement and Rehabilitation Program, Santana, Alfredo; Hospital Regional da Asa Norte, Pulmonolgy Cipriano, Graziella; University of Brasilia, 3- Rehabilitation Sciences and Health and Technologies in Health Sciences Program Oliveira, Miriã; UniEVANGELICA Centro Universitario de Anapolis, Human Movement and Rehabilitation Program Carrijo, Marilúcia de Morais; UniEVANGELICA Centro Universitario de Anapolis, Human Movement and Rehabilitation Program Lino, Maria Eduarda; UniEVANGELICA Centro Universitario de Anapolis, Human Movement and Rehabilitation Program Cahalin, Lawrence; University of Miami School of Medicine, Physical Therapy Lima, Alexandra; Hospital Regional da Asa Norte Borges, Robson; University of Brasilia, 3- Rehabilitation Sciences and Health and Technologies in Health Sciences Program santos, Dante; UniEVANGELICA Centro Universitario de Anapolis, Human Movement and Rehabilitation Program Silva , Iransé ; UniEVANGELICA Centro Universitario de Anapolis, Physical Education Oliveira, Luis Vicente; UniEVANGELICA Centro Universitario de Anapolis, Human Movement and Rehabilitation Program Cipriano, Gerson; Universidade de Brasília, Faculdade de Ceilândia
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	COVID-19, REHABILITATION MEDICINE, Public health < INFECTIOUS DISEASES

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ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COVID-19 (COVIDIMT): PROTOCOL FOR RANDOMIZED CONTROLLED DOUBLE-BLIND TRIAL.

Short Title: Inspiratory muscle training in COVID-19 patients

Vinicius Maldaner[1,2]; Jean Carlos Coutinho[1], Alfredo Nicodemos da Cruz Santana[2]; Graziella F. B. Cipriano[3], Miriã Cândida Oliveira[1], Marilúcia de Morais Carrijo[1], Maria Eduarda Moreira Lino[1], Lawrence P. Cahalin[4], Alexandra G.B Lima[3]; Robson Borges[3], Dante Brasil Santos[1]; Iransé Oliveira-Silva[1]; Luis Vicente Franco de Oliveira[1], Gerson Cipriano Jr[3];

Affiliations:

1- Human Movement and Rehabilitation Program, University Center of Anápolis UniEvangelica, Anápolis, Goiás, Brazil.
2- Hospital Regional da Asa Norte, HRAN, Brasília – Brazil.
3- Rehabilitation Sciences and Health and Technologies in Health Sciences Program, University of Brasilia, Brasilia, Federal District, Brazil.
4- Department of Physical Therapy, University of Miami Miller School of Medicine, Coral Gables, Florida, USA

Vinicius Maldaner – Conceived and designed the experiment

Jean Carlos Coutinho: - Investigation and Resources

Alfredo Nicodemos C. Santana: Original draft preparation.

Graziella FB Cipriano – Original Draft preparation

Miriã Cândida Oliveira – Pulmonary Rehabiliation Program

Marilúcia de Morais Carrijo – Pulmonary Rehabiliation Program

Maria Eduarda Moreira Lino – Pulmonary Rehabiliation Program

Lawrence Cahalin: Conceived and designed the experiment

Alexandra CGB Lima: Investigation and Resources

Robson Borges- Pulmonary Rehabiliation Program

Dante Brasil Santos – Investigation and Resources

Iransé Oliveira-Silva – Original Draft Preparation

Gerson Cipriano Jr - Conceived and designed the experiment

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Clinical Trial Registry: NCT04595097.

All authors have no conflicts to disclosure.

Corresponding Author:

Vinicius Maldaner

SQN 305 Bloco D apto 102 – Asa Norte – Brasília DF Brazil

PO BOX 70737-040

Phone Number: + 55 61 33688536

Email: viniciusmaldaner@gmail.com

WORD COUNT: 2854

ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COVID-19 (COVIDIMT): PROTOCOL FOR RANDOMIZED CONTROLLED DOUBLE-BLIND TRIAL.

ABSTRACT

Introduction: A significant number of patients with COVID-19 may experience dyspnea, anxiety, depression, pain, fatigue, and physical impairment symptoms, raising the need for a multidisciplinary rehabilitation approach, especially for those with advanced age, obesity, comorbidities, and organ failure. Traditional pulmonary rehabilitation (PR), including exercise training, psychosocial counselling, and education, has been employed to improve pulmonary function, exercise capacity, and quality of life in COVID-19 patients. However, the effects of inspiratory muscle training (IMT) in PR programs remain unclear. This study aims to determine whether the addition of a supervised-IMT in a PR is more effective than PR itself in improving dyspnea, health-related quality of life, and exercise capacity in symptomatic post-COVID-19 patients.

Method and Analysis: This parallel-group, assessor-blinded randomised controlled trial, powered for superiority, aims to assess exercise capacity as the primary outcome. A total of 120 are being recruited at three PR centers in Brazil. Following baseline testing, participants will be randomised using concealed allocation, to receive either: a) standard

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PR with sham IMT or b) standard PR added to IMT. Treatment effects or differences between the outcomes (at baseline, after 8- and 16- weeks, and after 6-months) of the study groups will be analysed using an ordinary two-way analysis of variance (ANOVA).

Ethics and Dissemination: This trial was approved by the Brazilian National Ethics Committee (CONEP) and received approval on 07/10/2020 (document number 4324069). The findings will be disseminated through publications in peer-reviewed journals and conference presentations.

Trial registration: This trial was prospectively registered in the Clinical Trials Registry NCT04595097

Key words: coronavirus, rehabilitation, breathing exercises.

Strengths and Limitations of this Study

- Evaluation of economic efficiency in addition to clinical effectiveness.
- The first fully powered study comparing inspiratory muscle training combined with pulmonary rehabilitation with sham inspiratory muscle training combined with pulmonary rehabilitation in post-COVID 19 patients.
- Full therapist blinding will be not possible.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has rapidly evolved into a global health emergency. The disease progression varies widely, with the patients exhibiting different symptoms such as hypoxia, dyspnea and fatigue (1). A significant number of patients with COVID-19 will have dyspnea, anxiety, depression, pain, fatigue, and physical impairment symptoms, which may be related to post intensive care syndrome (PICS) (2). The above symptoms and limitations of the PICS may persist for years, like in non-

COVID-19 acute respiratory distress syndrome patients. Persistent and late-onset symptoms in post-COVID-19 patients may persist for more than 120 days after symptom onset (3). Recent literature examining the consequences of infectious diseases like severe acute respiratory syndrome (SARS) and COVID-19 has identified respiratory muscle weakness and low exercise capacity that persists for a long time after the initial infection as residual effects (4).

Further research is needed to identify whether treatment strategies can reduce the duration of symptoms after COVID-19. Recent SARS-CoV-2 experience has revealed the need for a multidisciplinary rehabilitation approach, especially for patients with advanced age, obesity, comorbidities, and organ failure (5).

The International European Respiratory Society (ERS) and American Thoracic Society (ATS) Task Force suggest that COVID-19 survivors with a need for rehabilitative interventions at 6-8 weeks following hospital discharge should receive a comprehensive pulmonary rehabilitation (PR) program (6). Although most studies have evaluated the effects of PR in patients with chronic pulmonary obstructive disease (COPD), evidence suggests that it is a treatment option for other pulmonary conditions such as idiopathic pulmonary fibrosis (IPF) and COVID-19 (7, 8). PR has been advocated to provide comprehensive care, improve functional status, reduce symptoms, and decrease healthcare usage in patients with respiratory diseases. PR involves exercise training, psychosocial counseling, and education, and recently the ERS advocated that inspiratory muscle training (IMT) should be considered as an additional intervention in PR programs, especially in patients with inspiratory muscle weakness (9).

As dyspnea and fatigue are two of the most common late-onset symptoms of COVID-19, strategies to treat these symptoms should be encouraged. Langer et al. showed that 8 weeks of partially supervised IMT improved respiratory muscle strength and endurance, dyspnea, and exercise endurance in COPD subjects (10). A recent meta-analysis also demonstrated positive results for dyspnea and health-related quality of life in 362 patients with interstitial pulmonary fibrosis, associated with IMT with aerobic exercise (8). A recent review discussed the use of IMT in symptomatic patients with respiratory muscle weakness who are motivated to optimise their functional capacity gains through a PR

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program. Thus, randomised controlled trials should be conducted to examine the addition of IMT in PR programs in patients with exercise-induced dyspnea and low functional capacity.

Notably, few controlled clinical trials have investigated the addition of IMT in PR for patients after viral pneumonia illnesses, including COVID-19. In view of this fact, this trial aims to determine if supervised-IMT added to PR is more effective than PR alone in improving dyspnea, health-related quality of life, and exercise capacity in symptomatic post-COVID-19 patients. We hypothesise that the addition of IMR in PR programs will improve respiratory muscle strength, peak oxygen uptake, breathlessness and be cost-effective compared to traditional PR. This protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT guidance).

METHODS AND ANALYSIS

Study Design

This study's consists of a pragmatic randomised, double-blind controlled trial with two parallel groups (arms), conducted at three PR centres in the cities of Anapolis and Brasilia, Brazil. This protocol follows SPIRIT guidelines. A flowchart of the study protocol is shown in **Figure 1.**

Patient and Public involvement

Patients and the public will not be directly involved in the design, recruitment, or conduct of this study. They will be involved in our plans to disseminate the study results to participants and relevant community groups by assisting in the choice of what information/results to share and in what format.

Participants

Eligible participants will be identified through screening 4-6 weeks after ICU discharge. They Will be screened by pulmonologists of Long-Term COVID-19 Ambulatory in

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hospitals located in Brasilia and Anapolis. To be eligible, participants must be over 18 years of age with a confirmed COVID-19 diagnosis that required hospitalization and either i) non-invasive respiratory support (CPAP, high-flow oxygen catheter, non-breathing oxygen mask, or ii) invasive mechanical ventilation within three months of study recruitment. The exclusion criteria will include pregnancy, dependence on others to perform activities of daily living during the month prior to the latest ICU admission (gait aids are acceptable); documented cognitive impairment; proven or suspected spinal cord injury, or other neuromuscular diseases that will result in a permanent or prolonged weakness (not including ICU-acquired weakness); severe neurological disease; death being deemed inevitable as a result of the current illness; and unwillingness to commit to full active treatment either on the part of the patient or the treatment decision-maker.

For enrollment into the study, informed consent will be sought from the patients according to Brazil's federal laws.

Randomization and Allocation

Following informed consent and all baseline assessments, participants will be randomised at a 1:1 rate, according to the block randomisation generated by the (https://www.sealedenvelope.com) to either the first intervention group (PR combined with IMT) or the control group (PR combined with sham IMT). An independent researcher of the trial will prepare the randomisation schedule. The study registration in March 2021; the final registration will be in May 2022.

Ethics and Dissemination

The project was approved by the Brazilian National Ethics Committee and received approval on 07/10/2020 (document number 4324069). This trial was prospectively registered in the Clinical Trials Registry Platform on 20/10/2020 (NCT04595097); updated 12/04/2021. Patients will be invited to participate voluntarily. The results of this study will be reported in full through peer-reviewed journals and presented at scientific conferences. Significant protocol modifications will be communicated to the participants, trial registers, and journals. A copy of the informed consent form will be provided, if requested.

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Consent for Publication and Confidentiality

All information collected from the study participants will be kept confidential and stored in the laboratory's database during and after the trial. Only the researchers will assess the data to ensure anonymity and respect for human dignity and fulfil all the bioethics requirements of Resolution 466/2012 of the National Health Council and the Helsinki Declaration for research with humans.

Blinding

A trained physical therapist, blinded to the intervention allocation group, will perform all outcome assessments. One arm of the study will undergo a sham treatment (described below), which characterises the double-blind trial.

Interventions

The intervention consists of a supervised intervention with a workload of 50% to 60% of the maximal inspiratory pressure (MIP), including two sets of 30 breaths (60 breaths daily), with a 2-min interval in between work sets, 3 days per week, using a tapered flow-resistive loading (TFRL) device (POWERbreathe® KH2, HaB International Ltd, United Kingdom). This device was chosen mainly considering its visual feedback capability and the possibility of controlling the key training parameters (e.g., number of repetitions, external resistance, volume response, and work performed) during and after training sessions. It allows frequent re-assessment of the patient's training parameters for adjusting the training. The IMT program will be associated with a PR program, following a previously published protocol, for eight weeks.

Patients will be instructed and encouraged to perform 30 fast and effective inspirations and be allowed to pause if necessary, though not exceeding 1 min. The maximal inspiratory pressure (MIP) and maximal dynamic inspiratory pressure (S-Index) will be

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updated weekly to maintain the training load at the highest tolerable load, 50 to 60% of the most recent MIP. Individuals will perform weekly MIP assessments to ensure the correct load training. The same trained physiotherapist will perform all the respiratory muscle strength assessments. The training workload of the control group will be set at 10% of the baseline MIP and will not be modified throughout the intervention period (11). The IMT protocol will be performed after PR.

Both groups will perform the same PR program. The PR staff will prescribe a tailored individualised PR program within the pre-specified parameters recommended by the pulmonary rehabilitation guidelines. The PR will be delivered three times weekly, for 8 weeks (maximum 24 sessions [26 sessions total, including familiarisation sessions]), of 30 to 50 min supervised exercise sessions, with progressive and individualized multi-modal exercises (including both aerobic, strength training, and functional fitness modalities). An adequate 5-min warm-up and 5-min cool-down will be incorporated. According to previously determined ventilatory thresholds during a maximal cardiopulmonary exercise test, the intensity will be individually adjusted in the moderate domain and monitored by heart rate (HR) monitoring (10% range of the HR at first ventilatory threshold [1stVT]), rating of perceived exertion (4-6 in Borg scale), and oxygen saturation (above 90%), respectively.

Experienced physical therapists will perform familiarization sessions to optimize exercise prescription. The adherence to the PR program will be record in a daily log.

Measures

The initial assessment will be performed at the Pulmonology Department at Hospitals in Brasilia and Anápolis. Patients will receive a routine check-up, and if necessary, current medications will be optimised. Any changes to medication will be documented. Adverse events and complications during rehabilitation will be recorded by the physicians on a standardised basis in the medical survey sheet at the end of rehabilitation. Anthropometric and sociodemographic data will be collected in the first assessment.

Primary Outcome Measures

Cardiopulmonary exercise testing (CPX) Measurements

Subjects will undergo a maximum symptom-limited CPX, using cycle-ergometer ramp protocol (Corival, Lode, Netherlands) and ventilatory expired gas analysis cart (Quark CPET, Cosmed, Italy) following the recommendations of the European Respiratory Society for chronic lung diseases to obtain exercise capacity variables and respiratory efficiency. Volume and gas calibration will be performed before each test. Minute ventilation (VE), oxygen uptake (VO_2), and carbon dioxide output (VCO_2) will be acquired breath-by-breath and averaged over 10-second intervals. The ventilatory anaerobic threshold (VAT) will be determined using the V-slope method. Peak VO_2 will be expressed as the highest 10-second averaged sample obtained during the final plateau if the patient reached it, or the last 20 seconds of testing, if not. The ventilatory efficiency (VE/VCO_2 slope) will be calculated from a linear regression equation, from the start of the test to the exercise peak. The ventilatory reserve will be determined from the FEV_1 (calculated as 100- [VE (FEV1 x 40)100]). Circulatory power will be calculated from the VO_2 and systolic blood pressure product at the peak, and ventilatory power from the quotient of peak systolic blood pressure and VE/VCO_2 slope (12).

Secondary Outcomes

Dyspnea

Dyspnea will be assessed using the modified Medical Research Council Dyspnea Scale (mMRC). The mMRC is a 0-4 scale used to classify dyspnea's impact on physical function in patients with respiratory limitations. On mMRC, 0 represents a person who suffers from dyspnea only with strenuous exercise, while 4 represents a person who is too breathless to leave the house or breathless when dressing or undressing. We chose the mMRC because of its easy application, and other studies with COVID 19 have used it to assess dyspnea (4, 7).

Respiratory Muscle Strength

Respiratory muscle strength will be determined from residual volume using the technique proposed by Black and Hyatt to measure MIP and S-Index. Patients will be seated and motivated to perform a maximal voluntary exhalation effort at residual volume (RV), and

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then a verbal command will be given to perform a maximal inspiratory effort, according to ATS standards. The patients will be oriented to perform 10 maneuvers, with 60-second rest intervals between the maneuvers to avoid fatigue of the inspiratory muscles.

Inspiratory muscle endurance will be assessed using a timed inspiratory endurance test, which consists of breathing against a submaximal load (40% of MIP) provided by the device (KH2, POWERbreathe®, UK) until task failure (Tlim in seconds).

Anxiety and Depression

Anxiety and depression will be measured using the Hospital Anxiety and Depression Scale (HADS), a 14-item screening questionnaire from which an anxiety and depression subscale can be derived. Sub-score values > 5 points will identify increased symptoms of anxiety or depression; a total score > 9 will be considered indicative of psychological distress.

Health-related Quality of Life (HRQoL)

HRQoL will be assessed with the EQ-5D-3L instrument, which is recognised as a validated generic HRQoL measure consisting of five dimensions, each with five levels of response. Each answer combination will be converted into a health utility score.

The EQ-5D-3L tool has good test-retest reliability, is simple to use, and gives a single preference-based index value for health status that can be used for cost-effectiveness analysis.

Fatigue

Fatigue will be captured using the Fatigue Severity Scale (FSS), a nine-item questionnaire validated to evaluate disabling fatigue. Each item is rated on a 7-point scale ranging, from strongly disagree to strongly agree. A total score is derived from all nine questions; a higher score indicates a greater impact of fatigue on everyday activities.

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Pulmonary Function Testing (PFT)

Spirometry will be performed using a spirometer (Microlab 3.500; CareFusion, Yorba Linda, CA, USA). Three forced expiration maneuvers will be performed for validity and reproducibility purposes according to the ATS/ERS criteria, with patients sitting, in a room with controlled temperature, ambient pressure, and relative humidity. The following variables will be analyzed: (a) forced vital capacity (FVC, L), (b) forced expiratory volume in the first second (FEV_1, L), and c) FEV_1/FVC ratio (%). The obtained values will be recorded and compared to the predicted values for a Brazilian population.

Incremental Cost-utility Ratio (QALYs)

A cost-utility analysis (CUA) using the EQ-5D-3L responses will be performed to generate quality-adjusted life years (QALYs), which will generate an incremental cost per QALY. An economic evaluation will be undertaken to explore and determine the incremental costs and benefits of the IMT added to PR program over a 6-month time horizon. This follow-up period aims to capture the direct effects of the interventions and offer insights into outcomes and costs accrued in the months after the intervention is completed. Direct medical and overhead costs and indirect patient costs will be estimated. Direct costs were estimated using time-and-motion analysis, and included procedure personnel and supplies.

An incremental analysis will be undertaken to calculate the difference in costs and the difference in outcomes (improvements in effectiveness measures and QALYs) associated with the IMT and PR programs. QALYs will be calculated as the area under the curve connecting the utility scores reported at baseline and the subsequent follow-up points (13). The results will be presented in the form of incremental cost-effectiveness ratios, reflecting the extra cost for an additional unit of outcome. A sensitivity analysis will be performed to assess the robustness of the results to different values.

Adverse Events

Adverse events are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention, and any such event does not necessarily need to have a causal relationship with this intervention. It is

recognised that the patient population with a critical illness will experience several common signs and symptoms due to the severity of the underlying illness and the impact of standard therapies. These will not necessarily constitute an adverse event unless they are of concern or related to the study of the intervention in the investigator's clinical judgement. In all cases, the condition or disease underlying the symptoms, signs, or laboratory values should be reported, for example, tachycardia rather than chest palpitations. Following each intervention and outcome measure session, trial staff will be required to complete data entry forms indicating a severe or minor adverse event. In the case of serious adverse events, the study chief investigator will be notified immediately, participants will be managed appropriately, and the incident will be reported to the relevant hospital ethics committee. Adverse events will be collected from randomisation to 48 hours after cessation of our study protocol through phone calls.

Follow-up

Outcomes will be assessed at baseline, 8 weeks, 16 weeks and 6 months post-randomization. Figure 2 illustrates the schedule assessments of the participants. Patient-reported outcomes will also be collected during follow-up assessments. If any participant cannot attend the clinic, a postal questionnaire will be used to collect patient-reported outcomes.

Sample Size

Due to the lack of data on the effect of supervised-IMT in a PR in post-COVID-19 patients, we performed a power analysis based on a previous study on peak VO_2 measures after a PR program in patients with idiopathic pulmonary fibrosis (14). We used the software GPower® to calculate sample size with a priori analysis with an effect size of 0.19, an α error probability of 0.05, power (1- β error probability) of 0.80. Based on the results it was decided that 120 patients will be divided into two groups, with a dropout rate of 15%.

Data Analysis

Data will be summarised and reported following the CONSORT guidelines for RCTs, using intention-to-treat analyses (15). The Kolmogorov-Smirnov test will be used to analyse the normality of the sample's data. The patient baseline characteristics and outcome variables (both primary and secondary outcomes) will be summarised using descriptive measures of central tendency and dispersion for quantitative variables and absolute and relative frequencies for qualitative variables. Possible correlations will be assessed using Pearson or Spearman tests depending on the normality of the data. Associations will be performed using the X2 or Fischer's exact test. Treatment effects or differences between the outcomes (at baseline, after 8- and 16- weeks) of the study groups will be analyzed using an ordinary two-way analysis of variance (ANOVA), if the sample is parametric. If the sample has a non-parametric distribution, paired t-tests and an ordinary one-way ANOVA will be used. Intergroup analyses will be performed using the t-test or the Wilcoxon test, depending on the normality of the data.

Trial Managing and Data Monitoring

The trial management group, consisting of project staff and co-investigators involved in the day-to-day running of the trial, will meet monthly throughout the project to ensure data integrity, participant safety, and evaluation of any adverse events.

Deidentified data and statistical code will be made available on request soon after each report of the data has been published. Different aspects of the data will be published separately, which will determine when those data are made publicly available. A data-sharing agreement will require a commitment to using the data only for specified research purposes, securing the data appropriately and to destroying the data after a nominated period.

DISCUSSION

Patients with chronic respiratory symptoms commonly develop deconditioning and weakness of the respiratory muscles, which is related to dyspnea and exercise intolerance in this population (16). Inspiratory muscle training (IMT) may reduce neural respiratory drive and subsequently improve abnormal breathing patterns, which may equalise the relationship between respiratory muscle demand and energy supply to the respiratory

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muscles (17). Langer et al. demonstrated that an 8-week home-based IMT program improved inspiratory muscle strength and dyspnea, reducing diaphragm activation during maximal exercise, which may be associated with an important physiological response for the inspiratory muscles after IMT, which is compatible with the decrease in motor unit recruitment to generate a given force as a result of respiratory muscle hypertrophy (10).

While we acknowledge the value of traditional IMT protocols, that use mechanical loading devices, we believe that the IMT training with biofeedback provided by the POWERbreathe® KH2 device has the potential to provide additional clinical benefits because it can modulate all aspects of muscular performance, including strength, power and work capacity. The real-time biofeedback likely encourages the generation of higher pressures throughout a full inspiration, a feature that differs from other IMT methods. Thus, IMT via the POWERbreathe® KH2 device can facilitate a more controlled breathing pattern with an improved gas exchange during and after training.

Anastasio et al. investigated the mid-term impact of COVID-19 on respiratory function and functional capacity four months after infection and found respiratory muscle weakness, as reflected by the mean % predicted of MIP assessed in these patients (58%) (4). Moreover, both airway occlusion pressure (P 0.1) and P 0.1/MIP ratio were significantly lower in COVID-19 patients, indicating a possible neural drive impairment. A previous meta-analysis showed additional effects of IMT on clinically relevant outcomes in a sub-group of patients with respiratory muscle weakness (18). Another compelling fact is that addition of IMT could improve the attenuation of respiratory muscle metaboloreflex in these patients. The fatiguing contraction pattern could decrease locomotor muscle perfusion, with blood flow redistribution in favour of the respiratory muscles (19). This impairment may contribute to early peripheral muscle fatigue and lower exercise capacity. Therefore, strategies such as IMT that improve the capacity and dynamic function of the respiratory muscles should be effective in reducing dyspnea and might also improve the exercise capacity in patients with chronic respiratory diseases (17). Therefore, we believe that the use of IMT added to PR programs could improve the exercise capacity in post-COVID-19 patients.

The results of our study will provide valuable information for clinical practice. First, it will provide clinicians and rehabilitation practitioners information regarding the effects of exercise rehabilitation on chronic respiratory symptoms. Second, it will help healthcare

providers a cost-effectiveness analysis of the PR and IMT methods in COVID-19 patients; and third, patients with all viral types of pneumonia will be educated beforehand about the potential benefits or harmful effects of engaging in physical activity and exercise programs that include IMT, so that they can take an informed decision.

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FIGURE LEGENDS

Figure 1: Flow chart

Figure 2: Template of recommended content for the schedule of enrolment, interventions, and assessments

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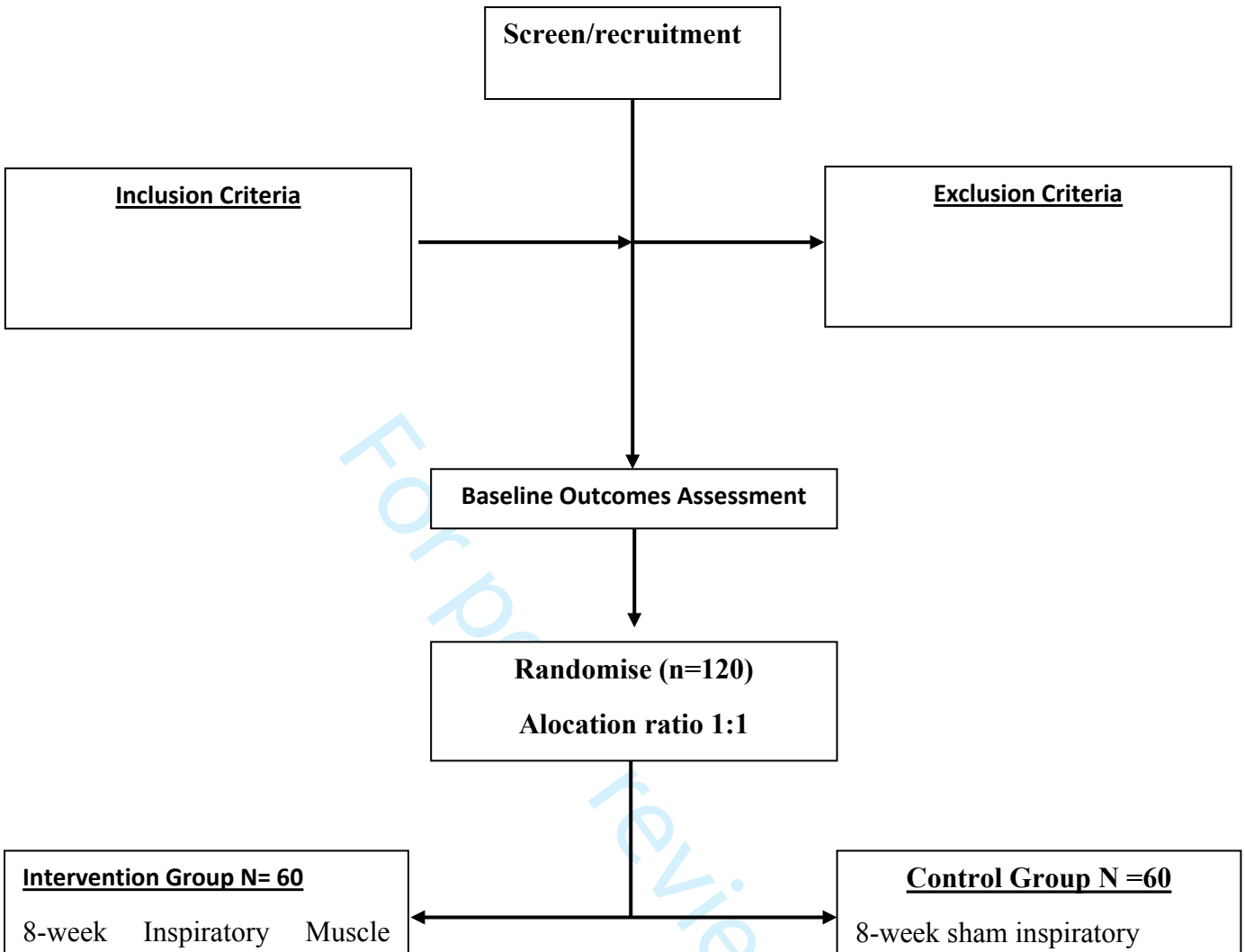

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Figure 2. **T**emplate of recommended content for the schedule of enrolment, interventions, and assessments.

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			
TIMEPOINT**	$-t_1$	0	t_1 *Baseline*	t_2 8 Weeks	*t3 16 weeks*	t_x *6 Months*
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
[IMT + Pulmonary Rehabilitation]			←	—		
[Sham IMT + Pulmonary Rehabilitation]			←	—		
ASSESSMENTS:						
[Clinical and Demographic Carachteristics]	X					
[Cardiopulmonary Exercise Testing]			X	X	X	
[mMRC]			X	X	X	
[EQ 5D 5L]			X	X	X	
HADS			X	X	X	
FSS			X	X	X	
Inspiratory Muscle Strength			X	X	X	
Inspiratory Muscle Endurance			X	X	X	
Cost-utility analysis						X

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Legends: IMT = inspiratory muscle training; mMRC = modified medical research council dyspnea scale; HADS = hospital anxiety and depression scale; FSS = fatigue severity scale.

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

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

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

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

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

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BMJ Open

ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COVID-19 (COVIDIMT): PROTOCOL FOR RANDOMIZED CONTROLLED DOUBLE-BLIND TRIAL.

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	COVID-19, REHABILITATION MEDICINE, Public health < INFECTIOUS DISEASES

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ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COVID-19 (COVIDIMT): PROTOCOL FOR RANDOMIZED CONTROLLED DOUBLE-BLIND TRIAL.

Short Title: Inspiratory muscle training in COVID-19 patients

Vinicius Maldaner[1,2]; Jean Carlos Coutinho[1], Alfredo Nicodemos da Cruz Santana[2]; Graziella F. B. Cipriano[3], Miriã Cândida Oliveira[1], Marilúcia de Morais Carrijo[1], Maria Eduarda Moreira Lino[1], Lawrence P. Cahalin[4], Alexandra G.B Lima[3]; Robson Borges[3], Dante Brasil Santos[1]; Iransé Oliveira-Silva[1]; Luis Vicente Franco de Oliveira[1], Gerson Cipriano Jr[3];

Affiliations:

1- Human Movement and Rehabilitation Program, University Center of Anápolis UniEvangelica, Anápolis, Goiás, Brazil.
2- Hospital Regional da Asa Norte, HRAN, Brasília – Brazil.
3- Rehabilitation Sciences and Health and Technologies in Health Sciences Program, University of Brasilia, Brasilia, Federal District, Brazil.
4- Department of Physical Therapy, University of Miami Miller School of Medicine, Coral Gables, Florida, USA

Vinicius Maldaner – Conceived and designed the experiment

Jean Carlos Coutinho: - Investigation and Resources

Alfredo Nicodemos C. Santana: Original draft preparation.

Graziella FB Cipriano – Original Draft preparation

Miriã Cândida Oliveira – Pulmonary Rehabiliation Program

Marilúcia de Morais Carrijo – Pulmonary Rehabiliation Program

Maria Eduarda Moreira Lino – Pulmonary Rehabiliation Program

Lawrence Cahalin: Conceived and designed the experiment

Alexandra CGB Lima: Investigation and Resources

Robson Borges- Pulmonary Rehabiliation Program

Dante Brasil Santos – Investigation and Resources

Iransé Oliveira-Silva – Original Draft Preparation

Luis Vicentre Franco de Oliveira- Original Draft Preparation

Gerson Cipriano Jr - Conceived and designed the experiment

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Corresponding Author:

Vinicius Maldaner

SQN 305 Bloco D apto 102 – Asa Norte – Brasília DF Brazil

PO BOX 70737-040

Phone Number: + 55 61 33688536

Email: viniciusmaldaner@gmail.com

WORD COUNT: 2854

ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COVID-19 (COVIDIMT): PROTOCOL FOR RANDOMIZED CONTROLLED DOUBLE-BLIND TRIAL.

ABSTRACT

Introduction: A significant number of patients with COVID-19 may experience dyspnea, anxiety, depression, pain, fatigue, and physical impairment symptoms, raising the need for a multidisciplinary rehabilitation approach, especially for those with advanced age, obesity, comorbidities, and organ failure. Traditional pulmonary rehabilitation (PR), including exercise training, psychosocial counselling, and education, has been employed to improve pulmonary function, exercise capacity, and quality of life in COVID-19 patients. However, the effects of inspiratory muscle training (IMT) in PR programs remain unclear. This study aims to determine whether the addition of a supervised-IMT in a PR is more effective than PR itself in improving dyspnea, health-related quality of life, and exercise capacity in symptomatic post-COVID-19 patients.

Method and Analysis: This parallel-group, assessor-blinded randomised controlled trial, powered for superiority, aims to assess exercise capacity as the primary outcome. A total

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of 120 are being recruited at three PR centers in Brazil. Following baseline testing, participants will be randomised using concealed allocation, to receive either: a) standard PR with sham IMT or b) standard PR added to IMT. Treatment effects or differences between the outcomes (at baseline, after 8- and 16- weeks, and after 6-months) of the study groups will be analysed using an ordinary two-way analysis of variance (ANOVA).
Ethics and Dissemination: This trial was approved by the Brazilian National Ethics Committee (CONEP) and received approval on 07/10/2020 (document number 4324069). The findings will be disseminated through publications in peer-reviewed journals and conference presentations.
Trial registration: This trial was prospectively registered in the Clinical Trials Registry NCT04595097

Key words: coronavirus, rehabilitation, breathing exercises.

Strengths and Limitations of this Study

- Evaluation of economic efficiency in addition to clinical effectiveness.
- The first fully powered study comparing inspiratory muscle training combined with pulmonary rehabilitation with sham inspiratory muscle training combined with pulmonary rehabilitation in post-COVID 19 patients.
- Full therapist blinding will be not possible.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has rapidly evolved into a global health emergency. The disease progression varies widely, with the patients exhibiting different symptoms such as hypoxia, dyspnea and fatigue (1). A significant number of patients with COVID-19 will have dyspnea, anxiety, depression, pain, fatigue, and physical

impairment symptoms, which may be related to post intensive care syndrome (PICS) (2). The above symptoms and limitations of the PICS may persist for years, like in non-COVID-19 acute respiratory distress syndrome patients. Persistent and late-onset symptoms in post-COVID-19 patients may persist for more than 120 days after symptom onset (3). Recent literature examining the consequences of infectious diseases like severe acute respiratory syndrome (SARS) and COVID-19 has identified respiratory muscle weakness and low exercise capacity that persists for a long time after the initial infection as residual effects (4).

Further research is needed to identify whether treatment strategies can reduce the duration of symptoms after COVID-19. Recent SARS-CoV-2 experience has revealed the need for a multidisciplinary rehabilitation approach, especially for patients with advanced age, obesity, comorbidities, and organ failure (5).

The International European Respiratory Society (ERS) and American Thoracic Society (ATS) Task Force suggest that COVID-19 survivors with a need for rehabilitative interventions at 6-8 weeks following hospital discharge should receive a comprehensive pulmonary rehabilitation (PR) program (6). Although most studies have evaluated the effects of PR in patients with chronic pulmonary obstructive disease (COPD), evidence suggests that it is a treatment option for other pulmonary conditions such as idiopathic pulmonary fibrosis (IPF) and COVID-19 (7, 8). PR has been advocated to provide comprehensive care, improve functional status, reduce symptoms, and decrease healthcare usage in patients with respiratory diseases. PR involves exercise training, psychosocial counseling, and education, and recently the ERS advocated that inspiratory muscle training (IMT) should be considered as an additional intervention in PR programs, especially in patients with inspiratory muscle weakness (9).

As dyspnea and fatigue are two of the most common late-onset symptoms of COVID-19, strategies to treat these symptoms should be encouraged. Langer et al. showed that 8 weeks of partially supervised IMT improved respiratory muscle strength and endurance, dyspnea, and exercise endurance in COPD subjects (10). A recent meta-analysis also demonstrated positive results for dyspnea and health-related quality of life in 362 patients with interstitial pulmonary fibrosis, associated with IMT with aerobic exercise (8). A

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recent review discussed the use of IMT in symptomatic patients with respiratory muscle weakness who are motivated to optimise their functional capacity gains through a PR program. Thus, randomised controlled trials should be conducted to examine the addition of IMT in PR programs in patients with exercise-induced dyspnea and low functional capacity.

Notably, few controlled clinical trials have investigated the addition of IMT in PR for patients after viral pneumonia illnesses, including COVID-19. In view of this fact, this trial aims to determine if supervised-IMT added to PR is more effective than PR alone in improving dyspnea, health-related quality of life, and exercise capacity in symptomatic post-COVID-19 patients. We hypothesise that the addition of IMT in PR programs will improve respiratory muscle strength, peak oxygen uptake, breathlessness and be cost-effective compared to traditional PR. This protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT guidance).

METHODS AND ANALYSIS

Study Design

This study's consists of a pragmatic randomised, double-blind controlled trial with two parallel groups (arms), conducted at three PR centres in the cities of Anapolis and Brasilia, Brazil. This protocol follows SPIRIT guidelines. A flowchart of the study protocol is shown in **Figure 1.**

Patient and Public involvement

Patients and the public will not be directly involved in the design, recruitment, or conduct of this study. They will be involved in our plans to disseminate the study results to participants and relevant community groups by assisting in the choice of what information/results to share and in what format.

Participants

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Eligible participants will be identified through screening 4-6 weeks after ICU discharge. They Will be screened by pulmonologists of Long-Term COVID-19 Ambulatory in hospitals located in Brasilia and Anapolis. To be eligible, participants must be over 18 years of age with a confirmed COVID-19 diagnosis that required hospitalization and either i) non-invasive respiratory support (CPAP, high-flow oxygen catheter, non-breathing oxygen mask, or ii) invasive mechanical ventilation within three months of study recruitment. The exclusion criteria will include pregnancy, dependence on others to perform activities of daily living during the month prior to the latest ICU admission (gait aids are acceptable); documented cognitive impairment; proven or suspected spinal cord injury, or other neuromuscular diseases that will result in a permanent or prolonged weakness (not including ICU-acquired weakness); severe neurological disease; death being deemed inevitable as a result of the current illness; and unwillingness to commit to full active treatment either on the part of the patient or the treatment decision-maker.

For enrollment into the study, informed consent will be sought from the patients according to Brazil's federal laws.

Randomization and Allocation

Following informed consent and all baseline assessments, participants will be randomised at a 1:1 rate, according to the block randomisation generated by the (https://www.sealedenvelope.com) to either the first intervention group (PR combined with IMT) or the control group (PR combined with sham IMT). An independent researcher of the trial will prepare the randomisation schedule. The study registration in March 2021; the final registration will be in May 2022.

Ethics and Dissemination

The project was approved by the Brazilian National Ethics Committee and received approval on 07/10/2020 (document number 4324069). This trial was prospectively registered in the Clinical Trials Registry Platform on 20/10/2020 (NCT04595097); updated 12/04/2021. Patients will be invited to participate voluntarily. The results of this study will be reported in full through peer-reviewed journals and presented at scientific conferences. Significant protocol modifications will be communicated to the participants,

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trial registers, and journals. A copy of the informed consent form will be provided, if requested.

Consent for Publication and Confidentiality

All information collected from the study participants will be kept confidential and stored in the laboratory's database during and after the trial. Only the researchers will assess the data to ensure anonymity and respect for human dignity and fulfil all the bioethics requirements of Resolution 466/2012 of the National Health Council and the Helsinki Declaration for research with humans.

Blinding

A trained physical therapist, blinded to the intervention allocation group, will perform all outcome assessments. One arm of the study will undergo a sham treatment (described below), which characterises the double-blind trial.

Interventions

The intervention consists of a supervised intervention with a workload of 50% to 60% of the maximal inspiratory pressure (MIP), including two sets of 30 breaths (60 breaths daily), with a 2-min interval in between work sets, 3 days per week, using a tapered flow-resistive loading (TFRL) device (POWERbreathe® KH2, HaB International Ltd, United Kingdom). This device was chosen mainly considering its visual feedback capability and the possibility of controlling the key training parameters (e.g., number of repetitions, external resistance, volume response, and work performed) during and after training sessions. It allows frequent re-assessment of the patient's training parameters for adjusting the training. The IMT program will be associated with a PR program, following a previously published protocol, for eight weeks.

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Patients will be instructed and encouraged to perform 30 fast and effective inspirations and be allowed to pause if necessary, though not exceeding 1 min. The maximal inspiratory pressure (MIP) and maximal dynamic inspiratory pressure (S-Index) will be updated weekly to maintain the training load at the highest tolerable load, 50 to 60% of the most recent MIP. Individuals will perform weekly MIP assessments to ensure the correct load training. The same trained physiotherapist will perform all the respiratory muscle strength assessments. The training workload of the control group will be set at 10% of the baseline MIP and will not be modified throughout the intervention period (11). The IMT protocol will be performed after PR.

Both groups will perform the same PR program. The PR staff will prescribe a tailored individualised PR program within the pre-specified parameters recommended by the pulmonary rehabilitation guidelines. The PR will be delivered three times weekly, for 8 weeks (maximum 24 sessions [26 sessions total, including familiarisation sessions]), of 30 to 50 min supervised exercise sessions, with progressive and individualized multi-modal exercises (including both aerobic, strength training, and functional fitness modalities). An adequate 5-min warm-up and 5-min cool-down will be incorporated. According to previously determined ventilatory thresholds during a maximal cardiopulmonary exercise test, the intensity will be individually adjusted in the moderate domain and monitored by heart rate (HR) monitoring (10% range of the HR at first ventilatory threshold [1stVT]), rating of perceived exertion (4-6 in Borg scale), and oxygen saturation (above 90%), respectively.

Experienced physical therapists will perform familiarization sessions to optimize exercise prescription. The adherence to the PR program will be record in a daily log.

Measures

The initial assessment will be performed at the Pulmonology Department at Hospitals in Brasilia and Anápolis. Patients will receive a routine check-up, and if necessary, current medications will be optimised. Any changes to medication will be documented. Adverse events and complications during rehabilitation will be recorded by the physicians on a standardised basis in the medical survey sheet at the end of rehabilitation. Anthropometric and sociodemographic data will be collected in the first assessment.

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Primary Outcome Measures

Cardiopulmonary exercise testing (CPX) Measurements

Subjects will undergo a maximum symptom-limited CPX, using cycle-ergometer ramp protocol (Corival, Lode, Netherlands) and ventilatory expired gas analysis cart (Quark CPET, Cosmed, Italy) following the recommendations of the European Respiratory Society for chronic lung diseases to obtain exercise capacity variables and respiratory efficiency. Volume and gas calibration will be performed before each test. Minute ventilation (VE), oxygen uptake (VO_2), and carbon dioxide output (VCO_2) will be acquired breath-by-breath and averaged over 10-second intervals. The ventilatory anaerobic threshold (VAT) will be determined using the V-slope method. Peak VO_2 will be expressed as the highest 10-second averaged sample obtained during the final plateau if the patient reached it, or the last 20 seconds of testing, if not. The ventilatory efficiency (VE/VCO_2 slope) will be calculated from a linear regression equation, from the start of the test to the exercise peak. The ventilatory reserve will be determined from the FEV_1 (calculated as 100- [VE (FEV1 x 40)100]). Circulatory power will be calculated from the VO_2 and systolic blood pressure product at the peak, and ventilatory power from the quotient of peak systolic blood pressure and VE/VCO_2 slope (12).

Secondary Outcomes

Dyspnea

Dyspnea will be assessed using the modified Medical Research Council Dyspnea Scale (mMRC). The mMRC is a 0-4 scale used to classify dyspnea's impact on physical function in patients with respiratory limitations. On mMRC, 0 represents a person who suffers from dyspnea only with strenuous exercise, while 4 represents a person who is too breathless to leave the house or breathless when dressing or undressing. We chose the mMRC because of its easy application, and other studies with COVID 19 have used it to assess dyspnea (4, 7).

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Respiratory Muscle Strength

Respiratory muscle strength will be determined from residual volume using the technique proposed by Black and Hyatt to measure MIP and S-Index. Patients will be seated and motivated to perform a maximal voluntary exhalation effort at residual volume (RV), and then a verbal command will be given to perform a maximal inspiratory effort, according to ATS standards (13). The patients will be oriented to perform 10 maneuvers, with 60-second rest intervals between the maneuvers to avoid fatigue of the inspiratory muscles.

Inspiratory muscle endurance will be assessed using a timed inspiratory endurance test, which consists of breathing against a submaximal load (40% of MIP) provided by the device (KH2, POWERbreathe®, UK) until task failure (Tlim in seconds).

Anxiety and Depression

Anxiety and depression will be measured using the Hospital Anxiety and Depression Scale (HADS), a 14-item screening questionnaire from which an anxiety and depression subscale can be derived. Sub-score values > 5 points will identify increased symptoms of anxiety or depression; a total score > 9 will be considered indicative of psychological distress (14).

Health-related Quality of Life (HRQoL)

HRQoL will be assessed with the EQ-5D-3L instrument, which is recognised as a validated generic HRQoL measure consisting of five dimensions, each with five levels of response. Each answer combination will be converted into a health utility score (15).

The EQ-5D-3L tool has good test-retest reliability, is simple to use, and gives a single preference-based index value for health status that can be used for cost-effectiveness analysis.

Fatigue

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Fatigue will be captured using the Fatigue Severity Scale (FSS), a nine-item questionnaire validated to evaluate disabling fatigue. Each item is rated on a 7-point scale ranging, from strongly disagree to strongly agree. A total score is derived from all nine questions; a higher score indicates a greater impact of fatigue on everyday activities (16).

Pulmonary Function Testing (PFT)

Spirometry will be performed using a spirometer (Microlab 3.500; CareFusion, Yorba Linda, CA, USA). Three forced expiration maneuvers will be performed for validity and reproducibility purposes according to the ATS/ERS criteria, with patients sitting, in a room with controlled temperature, ambient pressure, and relative humidity. The following variables will be analyzed: (a) forced vital capacity (FVC, L), (b) forced expiratory volume in the first second (FEV_1, L), and c) FEV_1/FVC ratio (%). The obtained values will be recorded and compared to the predicted values for a Brazilian population.

Incremental Cost-utility Ratio (QALYs)

A cost-utility analysis (CUA) using the EQ-5D-3L responses will be performed to generate quality-adjusted life years (QALYs), which will generate an incremental cost per QALY. An economic evaluation will be undertaken to explore and determine the incremental costs and benefits of the IMT added to PR program over a 6-month time horizon. This follow-up period aims to capture the direct effects of the interventions and offer insights into outcomes and costs accrued in the months after the intervention is completed. Direct medical and overhead costs and indirect patient costs will be estimated. Direct costs were estimated using time-and-motion analysis, and included procedure personnel and supplies.

An incremental analysis will be undertaken to calculate the difference in costs and the difference in outcomes (improvements in effectiveness measures and QALYs) associated with the IMT and PR programs. QALYs will be calculated as the area under the curve connecting the utility scores reported at baseline and the subsequent follow-up points (17). The results will be presented in the form of incremental cost-effectiveness ratios, reflecting the extra cost for an additional unit of outcome. A sensitivity analysis will be performed to assess the robustness of the results to different values.

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Adverse Events

Adverse events are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention, and any such event does not necessarily need to have a causal relationship with this intervention. It is recognised that the patient population with a critical illness will experience several common signs and symptoms due to the severity of the underlying illness and the impact of standard therapies. These will not necessarily constitute an adverse event unless they are of concern or related to the study of the intervention in the investigator's clinical judgement. In all cases, the condition or disease underlying the symptoms, signs, or laboratory values should be reported, for example, tachycardia rather than chest palpitations. Following each intervention and outcome measure session, trial staff will be required to complete data entry forms indicating a severe or minor adverse event. In the case of serious adverse events, the study chief investigator will be notified immediately, participants will be managed appropriately, and the incident will be reported to the relevant hospital ethics committee. Adverse events will be collected from randomisation to 48 hours after cessation of our study protocol through phone calls.

Follow-up

Outcomes will be assessed at baseline, 8 weeks, 16 weeks and 6 months post-randomization. Figure 2 illustrates the schedule assessments of the participants. Patient-reported outcomes will also be collected during follow-up assessments. If any participant cannot attend the clinic, a postal questionnaire will be used to collect patient-reported outcomes.

Sample Size

Due to the lack of data on the effect of supervised-IMT in a PR in post-COVID-19 patients, we performed a power analysis based on a previous meta-analysis of peak VO_2 in ml/kg/min in a combined PR and IMT program in patients with idiopathic pulmonary fibrosis (8). We used the software GPower® to calculate sample size with a priori analysis with an inter-groups difference of 2.0 ml/kg/min, a standard deviation (SD) of 3,5

ml/kg/min, an α error probability of 0.05, power (1- β error probability) of 0.80. Based on the results it was decided that 120 patients will be divided into two groups, with a dropout rate of 15%.

Data Analysis

Data will be summarised and reported following the CONSORT guidelines for RCTs, using intention-to-treat analyses (18). The Kolmogorov-Smirnov test will be used to analyse the normality of the sample's data. The patient baseline characteristics and outcome variables (both primary and secondary outcomes) will be summarised using descriptive measures of central tendency and dispersion for quantitative variables and absolute and relative frequencies for qualitative variables. Possible correlations will be assessed using Pearson or Spearman tests depending on the normality of the data. Associations will be performed using the X2 or Fischer's exact test. Treatment effects or differences between the outcomes (at baseline, after 8- and 16- weeks) of the study groups will be analyzed using an ordinary two-way analysis of variance (ANOVA), if the sample is parametric. If the sample has a non-parametric distribution, paired t-tests and an ordinary one-way ANOVA will be used. Intergroup analyses will be performed using the t-test or the Wilcoxon test, depending on the normality of the data.

Trial Managing and Data Monitoring

The trial management group, consisting of project staff and co-investigators involved in the day-to-day running of the trial, will meet monthly throughout the project to ensure data integrity, participant safety, and evaluation of any adverse events.

Deidentified data and statistical code will be made available on request soon after each report of the data has been published. Different aspects of the data will be published separately, which will determine when those data are made publicly available. A data-sharing agreement will require a commitment to using the data only for specified research purposes, securing the data appropriately and to destroying the data after a nominated period.

DISCUSSION

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Patients with chronic respiratory symptoms commonly develop deconditioning and weakness of the respiratory muscles, which is related to dyspnea and exercise intolerance in this population (19). Inspiratory muscle training (IMT) may reduce neural respiratory drive and subsequently improve abnormal breathing patterns, which may equalise the relationship between respiratory muscle demand and energy supply to the respiratory muscles (20). Langer et al. demonstrated that an 8-week home-based IMT program improved inspiratory muscle strength and dyspnea, reducing diaphragm activation during maximal exercise, which may be associated with an important physiological response for the inspiratory muscles after IMT, which is compatible with the decrease in motor unit recruitment to generate a given force as a result of respiratory muscle hypertrophy (10).

While we acknowledge the value of traditional IMT protocols, that use mechanical loading devices, we believe that the IMT training with biofeedback provided by the POWERbreathe® KH2 device has the potential to provide additional clinical benefits because it can modulate all aspects of muscular performance, including strength, power and work capacity. The real-time biofeedback likely encourages the generation of higher pressures throughout a full inspiration, a feature that differs from other IMT methods. Thus, IMT via the POWERbreathe® KH2 device can facilitate a more controlled breathing pattern with an improved gas exchange during and after training.

Anastasio et al. investigated the mid-term impact of COVID-19 on respiratory function and functional capacity four months after infection and found respiratory muscle weakness, as reflected by the mean % predicted of MIP assessed in these patients (58%) (4). Moreover, both airway occlusion pressure (P 0.1) and P 0.1/MIP ratio were significantly lower in COVID-19 patients, indicating a possible neural drive impairment. A previous meta-analysis showed additional effects of IMT on clinically relevant outcomes in a sub-group of patients with respiratory muscle weakness (21). Another compelling fact is that addition of IMT could improve the attenuation of respiratory muscle metaboloreflex in these patients. The fatiguing contraction pattern could decrease locomotor muscle perfusion, with blood flow redistribution in favour of the respiratory muscles (22). This impairment may contribute to early peripheral muscle fatigue and lower exercise capacity. Therefore, strategies such as IMT that improve the capacity and dynamic function of the respiratory muscles should be effective in reducing dyspnea and might also improve the exercise capacity in patients with chronic respiratory diseases

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(20). Therefore, we believe that the use of IMT added to PR programs could improve the exercise capacity in post-COVID-19 patients.

The results of our study will provide valuable information for clinical practice. First, it will provide clinicians and rehabilitation practitioners information regarding the effects of exercise rehabilitation on chronic respiratory symptoms. Second, it will help healthcare providers a cost-effectiveness analysis of the PR and IMT methods in COVID-19 patients; and third, patients with all viral types of pneumonia will be educated beforehand about the potential benefits or harmful effects of engaging in physical activity and exercise programs that include IMT, so that they can take an informed decision.

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FIGURE LEGENDS

Figure 1: Flow chart

Figure 2: Template of recommended content for the schedule of enrolment, interventions, and assessments

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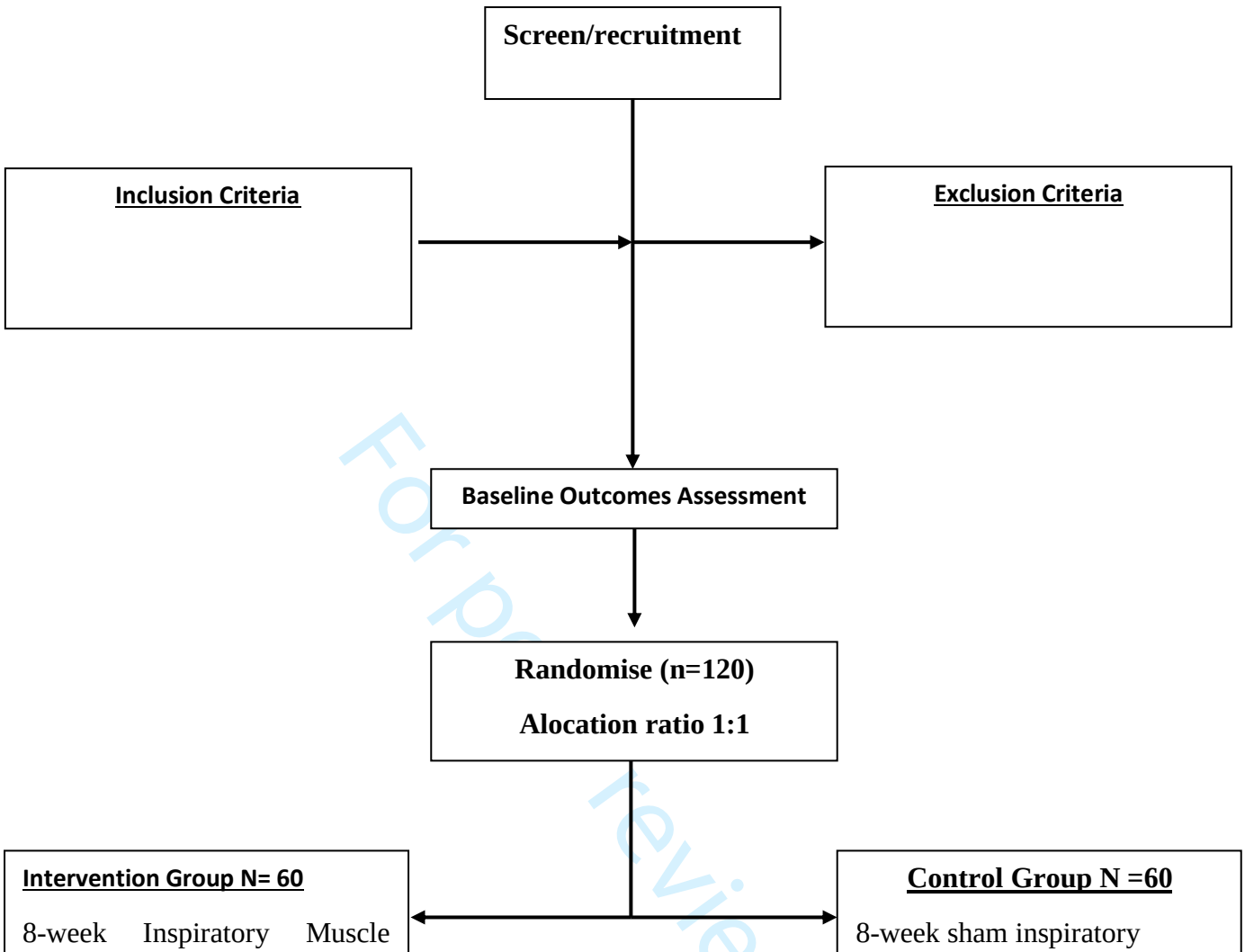

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Figure 2. **T**emplate of recommended content for the schedule of enrolment, interventions, and assessments.

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			
TIMEPOINT**	***-t_1***	**0**	***t_1*** *Baseline*	***t_2*** **8 Weeks**	***t3 16 weeks***	***t_x*** ***6 Months***
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
[IMT + Pulmonary Rehabilitation]			←	—		
[Sham IMT + Pulmonary Rehabilitation]			←	—		
ASSESSMENTS:						
[Clinical and Demographic Carachteristics]	X					
[Cardiopulmonary Exercise Testing]			X	X	X	
[mMRC]			X	X	X	
[EQ 5D 5L]			X	X	X	
HADS			X	X	X	
FSS			X	X	X	
Inspiratory Muscle Strength			X	X	X	
Inspiratory Muscle Endurance			X	X	X	
Cost-utility analysis						X

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Legends: IMT = inspiratory muscle training; mMRC = modified medical research council dyspnea scale; HADS = hospital anxiety and depression scale; FSS = fatigue severity scale.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	ok
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	ok

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

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BMJ Open

ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COVID-19 (COVIDIMT): PROTOCOL FOR RANDOMIZED CONTROLLED DOUBLE-BLIND TRIAL.

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	COVID-19, REHABILITATION MEDICINE, Public health < INFECTIOUS DISEASES

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Manuscripts

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ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COVID-19 (COVIDIMT): PROTOCOL FOR RANDOMIZED CONTROLLED DOUBLE-BLIND TRIAL.

Short Title: Inspiratory muscle training in COVID-19 patients

Vinicius Maldaner[1,2]; Jean Carlos Coutinho[1], Alfredo Nicodemos da Cruz Santana[2]; Graziella F. B. Cipriano[3], Miriã Cândida Oliveira[1], Marilúcia de Morais Carrijo[1], Maria Eduarda Moreira Lino[1], Lawrence P. Cahalin[4], Alexandra G.B Lima[3]; Robson Borges[3], Dante Brasil Santos[1]; Iransé Oliveira-Silva[1]; Luis Vicente Franco de Oliveira[1], Gerson Cipriano Jr[3];

Affiliations:

1- Human Movement and Rehabilitation Program, University Center of Anápolis UniEvangelica, Anápolis, Goiás, Brazil.
2- Hospital Regional da Asa Norte, HRAN, Brasília – Brazil.
3- Rehabilitation Sciences and Health and Technologies in Health Sciences Program, University of Brasilia, Brasilia, Federal District, Brazil.
4- Department of Physical Therapy, University of Miami Miller School of Medicine, Coral Gables, Florida, USA

Clinical Trial Registry: NCT04595097.

All authors have no conflicts to disclosure.

Corresponding Author:

Vinicius Maldaner

SQN 305 Bloco D apto 102 – Asa Norte – Brasília DF Brazil

PO BOX 70737-040

Phone Number: + 55 61 33688536

Email: viniciusmaldaner@gmail.com

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ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COVID-19 (COVIDIMT): PROTOCOL FOR RANDOMIZED CONTROLLED DOUBLE-BLIND TRIAL.

ABSTRACT

Introduction: A significant number of patients with COVID-19 may experience dyspnea, anxiety, depression, pain, fatigue, and physical impairment symptoms, raising the need for a multidisciplinary rehabilitation approach, especially for those with advanced age, obesity, comorbidities, and organ failure. Traditional pulmonary rehabilitation (PR), including exercise training, psychosocial counselling, and education, has been employed to improve pulmonary function, exercise capacity, and quality of life in COVID-19 patients. However, the effects of inspiratory muscle training (IMT) in PR programs remain unclear. This study aims to determine whether the addition of a supervised-IMT in a PR is more effective than PR itself in improving dyspnea, health-related quality of life, and exercise capacity in symptomatic post-COVID-19 patients.

Method and Analysis: This parallel-group, assessor-blinded randomised controlled trial, powered for superiority, aims to assess exercise capacity as the primary outcome. A total of 120 are being recruited at three PR centers in Brazil. Following baseline testing, participants will be randomised using concealed allocation, to receive either: a) standard PR with sham IMT or b) standard PR added to IMT. Treatment effects or differences between the outcomes (at baseline, after 8- and 16- weeks, and after 6-months) of the study groups will be analysed using an ordinary two-way analysis of variance (ANOVA).

Ethics and Dissemination: This trial was approved by the Brazilian National Ethics Committee (CONEP) and received approval on 07/10/2020 (document number 4324069). The findings will be disseminated through publications in peer-reviewed journals and conference presentations.

Trial registration: This trial was prospectively registered in the Clinical Trials Registry NCT04595097

Key words: coronavirus, rehabilitation, breathing exercises.

Strengths and Limitations of this Study

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- Evaluation of economic efficiency in addition to clinical effectiveness.
- The first fully powered study comparing inspiratory muscle training combined with pulmonary rehabilitation with sham inspiratory muscle training combined with pulmonary rehabilitation in post-COVID 19 patients.
- Full therapist blinding will be not possible.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has rapidly evolved into a global health emergency. The disease progression varies widely, with the patients exhibiting different symptoms such as hypoxia, dyspnea and fatigue (1). A significant number of patients with COVID-19 will have dyspnea, anxiety, depression, pain, fatigue, and physical impairment symptoms, which may be related to post intensive care syndrome (PICS) (2). The above symptoms and limitations of the PICS may persist for years, like in non-COVID-19 acute respiratory distress syndrome patients. Persistent and late-onset symptoms in post-COVID-19 patients may persist for more than 120 days after symptom onset (3). Recent literature examining the consequences of infectious diseases like severe acute respiratory syndrome (SARS) and COVID-19 has identified respiratory muscle weakness and low exercise capacity that persists for a long time after the initial infection as residual effects (4).

Further research is needed to identify whether treatment strategies can reduce the duration of symptoms after COVID-19. Recent SARS-CoV-2 experience has revealed the need for a multidisciplinary rehabilitation approach, especially for patients with advanced age, obesity, comorbidities, and organ failure (5).

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The International European Respiratory Society (ERS) and American Thoracic Society (ATS) Task Force suggest that COVID-19 survivors with a need for rehabilitative interventions at 6-8 weeks following hospital discharge should receive a comprehensive pulmonary rehabilitation (PR) program (6). Although most studies have evaluated the effects of PR in patients with chronic pulmonary obstructive disease (COPD), evidence suggests that it is a treatment option for other pulmonary conditions such as idiopathic pulmonary fibrosis (IPF) and COVID-19 (7, 8). PR has been advocated to provide comprehensive care, improve functional status, reduce symptoms, and decrease healthcare usage in patients with respiratory diseases. PR involves exercise training, psychosocial counseling, and education, and recently the ERS advocated that inspiratory muscle training (IMT) should be considered as an additional intervention in PR programs, especially in patients with inspiratory muscle weakness (9).

As dyspnea and fatigue are two of the most common late-onset symptoms of COVID-19, strategies to treat these symptoms should be encouraged. Langer et al. showed that 8 weeks of partially supervised IMT improved respiratory muscle strength and endurance, dyspnea, and exercise endurance in COPD subjects (10). A recent meta-analysis also demonstrated positive results for dyspnea and health-related quality of life in 362 patients with interstitial pulmonary fibrosis, associated with IMT with aerobic exercise (8). A recent review discussed the use of IMT in symptomatic patients with respiratory muscle weakness who are motivated to optimise their functional capacity gains through a PR program. Thus, randomised controlled trials should be conducted to examine the addition of IMT in PR programs in patients with exercise-induced dyspnea and low functional capacity.

Notably, few controlled clinical trials have investigated the addition of IMT in PR for patients after viral pneumonia illnesses, including COVID-19. In view of this fact, this trial aims to determine if supervised-IMT added to PR is more effective than PR alone in improving dyspnea, health-related quality of life, and exercise capacity in symptomatic post-COVID-19 patients. We hypothesise that the addition of IMT in PR programs will improve respiratory muscle strength, peak oxygen uptake, breathlessness and be cost-effective compared to traditional PR. This protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT guidance).

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METHODS AND ANALYSIS

Study Design

This study's consists of a pragmatic randomised, double-blind controlled trial with two parallel groups (arms), conducted at three PR centres in the cities of Anapolis and Brasilia, Brazil. This protocol follows SPIRIT guidelines. A flowchart of the study protocol is shown in **Figure 1.**

Patient and Public involvement

Patients and the public will not be directly involved in the design, recruitment, or conduct of this study. They will be involved in our plans to disseminate the study results to participants and relevant community groups by assisting in the choice of what information/results to share and in what format.

Participants

Eligible participants will be identified through screening 4-6 weeks after ICU discharge. They Will be screened by pulmonologists of Long-Term COVID-19 Ambulatory in hospitals located in Brasilia and Anapolis. To be eligible, participants must be over 18 years of age with a confirmed COVID-19 diagnosis that required hospitalization and either i) non-invasive respiratory support (CPAP, high-flow oxygen catheter, non-breathing oxygen mask, or ii) invasive mechanical ventilation within three months of study recruitment. The exclusion criteria will include pregnancy, dependence on others to perform activities of daily living during the month prior to the latest ICU admission (gait aids are acceptable); documented cognitive impairment; proven or suspected spinal cord injury, or other neuromuscular diseases that will result in a permanent or prolonged weakness (not including ICU-acquired weakness); severe neurological disease; death being deemed inevitable as a result of the current illness; and unwillingness to commit to full active treatment either on the part of the patient or the treatment decision-maker.

For enrollment into the study, informed consent will be sought from the patients according to Brazil's federal laws.

Randomization and Allocation

Following informed consent and all baseline assessments, participants will be randomised at a 1:1 rate, according to the block randomisation generated by the (https://www.sealedenvelope.com) to either the first intervention group (PR combined with IMT) or the control group (PR combined with sham IMT). An independent researcher of the trial will prepare the randomisation schedule. The study registration in March 2021; the final registration will be in May 2022.

Ethics and Dissemination

The project was approved by the Brazilian National Ethics Committee and received approval on 07/10/2020 (document number 4324069). This trial was prospectively registered in the Clinical Trials Registry Platform on 20/10/2020 (NCT04595097); updated 12/04/2021. Patients will be invited to participate voluntarily. The results of this study will be reported in full through peer-reviewed journals and presented at scientific conferences. Significant protocol modifications will be communicated to the participants, trial registers, and journals. A copy of the informed consent form will be provided, if requested.

Consent for Publication and Confidentiality

All information collected from the study participants will be kept confidential and stored in the laboratory's database during and after the trial. Only the researchers will assess the data to ensure anonymity and respect for human dignity and fulfil all the bioethics requirements of Resolution 466/2012 of the National Health Council and the Helsinki Declaration for research with humans.

Blinding

A trained physical therapist, blinded to the intervention allocation group, will perform all outcome assessments. One arm of the study will undergo a sham treatment (described below), which characterises the double-blind trial.

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Interventions

The intervention consists of a supervised intervention with a workload of 50% to 60% of the maximal inspiratory pressure (MIP), including two sets of 30 breaths (60 breaths daily), with a 2-min interval in between work sets, 3 days per week, using a tapered flow-resistive loading (TFRL) device (POWERbreathe® KH2, HaB International Ltd, United Kingdom). This device was chosen mainly considering its visual feedback capability and the possibility of controlling the key training parameters (e.g., number of repetitions, external resistance, volume response, and work performed) during and after training sessions. It allows frequent re-assessment of the patient's training parameters for adjusting the training. The IMT program will be associated with a PR program, following a previously published protocol, for eight weeks.

Patients will be instructed and encouraged to perform 30 fast and effective inspirations and be allowed to pause if necessary, though not exceeding 1 min. The maximal inspiratory pressure (MIP) and maximal dynamic inspiratory pressure (S-Index) will be updated weekly to maintain the training load at the highest tolerable load, 50 to 60% of the most recent MIP. Individuals will perform weekly MIP assessments to ensure the correct load training. The same trained physiotherapist will perform all the respiratory muscle strength assessments. The training workload of the control group will be set at 10% of the baseline MIP and will not be modified throughout the intervention period (11). The IMT protocol will be performed after PR.

Both groups will perform the same PR program. The PR staff will prescribe a tailored individualised PR program within the pre-specified parameters recommended by the pulmonary rehabilitation guidelines. The PR will be delivered three times weekly, for 8 weeks (maximum 24 sessions [26 sessions total, including familiarisation sessions]), of 30 to 50 min supervised exercise sessions, with progressive and individualized multi-modal exercises (including both aerobic, strength training, and functional fitness

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modalities). An adequate 5-min warm-up and 5-min cool-down will be incorporated. According to previously determined ventilatory thresholds during a maximal cardiopulmonary exercise test, the intensity will be individually adjusted in the moderate domain and monitored by heart rate (HR) monitoring (10% range of the HR at first ventilatory threshold [1stVT]), rating of perceived exertion (4-6 in Borg scale), and oxygen saturation (above 90%), respectively.

Experienced physical therapists will perform familiarization sessions to optimize exercise prescription. The adherence to the PR program will be record in a daily log.

Measures

The initial assessment will be performed at the Pulmonology Department at Hospitals in Brasilia and Anápolis. Patients will receive a routine check-up, and if necessary, current medications will be optimised. Any changes to medication will be documented. Adverse events and complications during rehabilitation will be recorded by the physicians on a standardised basis in the medical survey sheet at the end of rehabilitation. Anthropometric and sociodemographic data will be collected in the first assessment.

Primary Outcome Measures

Cardiopulmonary exercise testing (CPX) Measurements

Subjects will undergo a maximum symptom-limited CPX, using cycle-ergometer ramp protocol (Corival, Lode, Netherlands) and ventilatory expired gas analysis cart (Quark CPET, Cosmed, Italy) following the recommendations of the European Respiratory Society for chronic lung diseases to obtain exercise capacity variables and respiratory efficiency. Volume and gas calibration will be performed before each test. Minute ventilation (VE), oxygen uptake (VO_2), and carbon dioxide output (VCO_2) will be acquired breath-by-breath and averaged over 10-second intervals. The ventilatory anaerobic threshold (VAT) will be determined using the V-slope method. Peak VO_2 will be expressed as the highest 10-second averaged sample obtained during the final plateau if the patient reached it, or the last 20 seconds of testing, if not. The ventilatory efficiency (VE/VCO_2 slope) will be calculated from a linear regression equation, from the start of the test to the exercise peak. The ventilatory reserve will be determined from the FEV_1

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(calculated as 100- [VE (FEV1 x 40)100]). Circulatory power will be calculated from the VO_2 and systolic blood pressure product at the peak, and ventilatory power from the quotient of peak systolic blood pressure and VE/VCO_2 slope (12).

Secondary Outcomes

Dyspnea

Dyspnea will be assessed using the modified Medical Research Council Dyspnea Scale (mMRC). The mMRC is a 0-4 scale used to classify dyspnea's impact on physical function in patients with respiratory limitations. On mMRC, 0 represents a person who suffers from dyspnea only with strenuous exercise, while 4 represents a person who is too breathless to leave the house or breathless when dressing or undressing. We chose the mMRC because of its easy application, and other studies with COVID 19 have used it to assess dyspnea (4, 7).

Respiratory Muscle Strength

Respiratory muscle strength will be determined from residual volume using the technique proposed by Black and Hyatt to measure MIP and S-Index. Patients will be seated and motivated to perform a maximal voluntary exhalation effort at residual volume (RV), and then a verbal command will be given to perform a maximal inspiratory effort, according to ATS standards (13). The patients will be oriented to perform 10 maneuvers, with 60-second rest intervals between the maneuvers to avoid fatigue of the inspiratory muscles.

Inspiratory muscle endurance will be assessed using a timed inspiratory endurance test, which consists of breathing against a submaximal load (40% of MIP) provided by the device (KH2, POWERbreathe®, UK) until task failure (Tlim in seconds).

Anxiety and Depression

Anxiety and depression will be measured using the Hospital Anxiety and Depression Scale (HADS), a 14-item screening questionnaire from which an anxiety and depression

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subscale can be derived. Sub-score values > 5 points will identify increased symptoms of anxiety or depression; a total score > 9 will be considered indicative of psychological distress (14).

Health-related Quality of Life (HRQoL)

HRQoL will be assessed with the EQ-5D-3L instrument, which is recognised as a validated generic HRQoL measure consisting of five dimensions, each with five levels of response. Each answer combination will be converted into a health utility score (15).

The EQ-5D-3L tool has good test-retest reliability, is simple to use, and gives a single preference-based index value for health status that can be used for cost-effectiveness analysis.

Fatigue

Fatigue will be captured using the Fatigue Severity Scale (FSS), a nine-item questionnaire validated to evaluate disabling fatigue. Each item is rated on a 7-point scale ranging, from strongly disagree to strongly agree. A total score is derived from all nine questions; a higher score indicates a greater impact of fatigue on everyday activities (16).

Pulmonary Function Testing (PFT)

Spirometry will be performed using a spirometer (Microlab 3.500; CareFusion, Yorba Linda, CA, USA). Three forced expiration maneuvers will be performed for validity and reproducibility purposes according to the ATS/ERS criteria, with patients sitting, in a room with controlled temperature, ambient pressure, and relative humidity. The following variables will be analyzed: (a) forced vital capacity (FVC, L), (b) forced expiratory volume in the first second (FEV_1, L), and c) FEV_1/FVC ratio (%). The obtained values will be recorded and compared to the predicted values for a Brazilian population.

Incremental Cost-utility Ratio (QALYs)

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A cost-utility analysis (CUA) using the EQ-5D-3L responses will be performed to generate quality-adjusted life years (QALYs), which will generate an incremental cost per QALY. An economic evaluation will be undertaken to explore and determine the incremental costs and benefits of the IMT added to PR program over a 6-month time horizon. This follow-up period aims to capture the direct effects of the interventions and offer insights into outcomes and costs accrued in the months after the intervention is completed. Direct medical and overhead costs and indirect patient costs will be estimated. Direct costs were estimated using time-and-motion analysis, and included procedure personnel and supplies.

An incremental analysis will be undertaken to calculate the difference in costs and the difference in outcomes (improvements in effectiveness measures and QALYs) associated with the IMT and PR programs. QALYs will be calculated as the area under the curve connecting the utility scores reported at baseline and the subsequent follow-up points (17). The results will be presented in the form of incremental cost-effectiveness ratios, reflecting the extra cost for an additional unit of outcome. A sensitivity analysis will be performed to assess the robustness of the results to different values.

Adverse Events

Adverse events are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention, and any such event does not necessarily need to have a causal relationship with this intervention. It is recognised that the patient population with a critical illness will experience several common signs and symptoms due to the severity of the underlying illness and the impact of standard therapies. These will not necessarily constitute an adverse event unless they are of concern or related to the study of the intervention in the investigator's clinical judgement. In all cases, the condition or disease underlying the symptoms, signs, or laboratory values should be reported, for example, tachycardia rather than chest palpitations. Following each intervention and outcome measure session, trial staff will be required to complete data entry forms indicating a severe or minor adverse event. In the case of serious adverse events, the study chief investigator will be notified immediately, participants will be managed appropriately, and the incident will be reported to the

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relevant hospital ethics committee. Adverse events will be collected from randomisation to 48 hours after cessation of our study protocol through phone calls.

Follow-up

Outcomes will be assessed at baseline, 8 weeks, 16 weeks and 6 months post-randomization. Figure 2 illustrates the schedule assessments of the participants. Patient-reported outcomes will also be collected during follow-up assessments. If any participant cannot attend the clinic, a postal questionnaire will be used to collect patient-reported outcomes.

Sample Size

Due to the lack of data on the effect of supervised-IMT in a PR in post-COVID-19 patients, we performed a power analysis based on a previous meta-analysis of peak VO_2 in ml/kg/min in patients with idiopathic pulmonary fibrosis (18). We used the software GPower® to calculate sample size with a priori analysis with an inter-groups difference of 1.46 ml/kg/min, a standard deviation (SD) of 3,5 ml/kg/min, an α error probability of 0.05, power (1- β error probability) of 0.80. Based on the results it was decided that 138 patients will be divided into two groups, with a dropout rate of 15%.

Data Analysis

Data will be summarised and reported following the CONSORT guidelines for RCTs, using intention-to-treat analyses (19). The Kolmogorov-Smirnov test will be used to analyse the normality of the sample's data. The patient baseline characteristics and outcome variables (both primary and secondary outcomes) will be summarised using descriptive measures of central tendency and dispersion for quantitative variables and absolute and relative frequencies for qualitative variables. Possible correlations will be assessed using Pearson or Spearman tests depending on the normality of the data. Associations will be performed using the X2 or Fischer's exact test. Treatment effects or differences between the outcomes (at baseline, after 8- and 16- weeks) of the study groups will be analyzed using an ordinary two-way analysis of variance (ANOVA), if the sample is parametric. If the sample has a non-parametric distribution, paired t-tests and an

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ordinary one-way ANOVA will be used. Intergroup analyses will be performed using the t-test or the Wilcoxon test, depending on the normality of the data.

Trial Managing and Data Monitoring

The trial management group, consisting of project staff and co-investigators involved in the day-to-day running of the trial, will meet monthly throughout the project to ensure data integrity, participant safety, and evaluation of any adverse events.

Deidentified data and statistical code will be made available on request soon after each report of the data has been published. Different aspects of the data will be published separately, which will determine when those data are made publicly available. A data-sharing agreement will require a commitment to using the data only for specified research purposes, securing the data appropriately and to destroying the data after a nominated period.

DISCUSSION

Patients with chronic respiratory symptoms commonly develop deconditioning and weakness of the respiratory muscles, which is related to dyspnea and exercise intolerance in this population (20). Inspiratory muscle training (IMT) may reduce neural respiratory drive and subsequently improve abnormal breathing patterns, which may equalise the relationship between respiratory muscle demand and energy supply to the respiratory muscles (21). Langer et al. demonstrated that an 8-week home-based IMT program improved inspiratory muscle strength and dyspnea, reducing diaphragm activation during maximal exercise, which may be associated with an important physiological response for the inspiratory muscles after IMT, which is compatible with the decrease in motor unit recruitment to generate a given force as a result of respiratory muscle hypertrophy (10).

While we acknowledge the value of traditional IMT protocols, that use mechanical loading devices, we believe that the IMT training with biofeedback provided by the POWERbreathe® KH2 device has the potential to provide additional clinical benefits because it can modulate all aspects of muscular performance, including strength, power and work capacity. The real-time biofeedback likely encourages the generation of higher

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pressures throughout a full inspiration, a feature that differs from other IMT methods. Thus, IMT via the POWERbreathe® KH2 device can facilitate a more controlled breathing pattern with an improved gas exchange during and after training.

Anastasio et al. investigated the mid-term impact of COVID-19 on respiratory function and functional capacity four months after infection and found respiratory muscle weakness, as reflected by the mean % predicted of MIP assessed in these patients (58%) (4). Moreover, both airway occlusion pressure (P 0.1) and P 0.1/MIP ratio were significantly lower in COVID-19 patients, indicating a possible neural drive impairment. A previous meta-analysis showed additional effects of IMT on clinically relevant outcomes in a sub-group of patients with respiratory muscle weakness (22). Another compelling fact is that addition of IMT could improve the attenuation of respiratory muscle metaboloreflex in these patients. The fatiguing contraction pattern could decrease locomotor muscle perfusion, with blood flow redistribution in favour of the respiratory muscles (23). This impairment may contribute to early peripheral muscle fatigue and lower exercise capacity. Therefore, strategies such as IMT that improve the capacity and dynamic function of the respiratory muscles should be effective in reducing dyspnea and might also improve the exercise capacity in patients with chronic respiratory diseases (21). Therefore, we believe that the use of IMT added to PR programs could improve the exercise capacity in post-COVID-19 patients.

The results of our study will provide valuable information for clinical practice. First, it will provide clinicians and rehabilitation practitioners information regarding the effects of exercise rehabilitation on chronic respiratory symptoms. Second, it will help healthcare providers a cost-effectiveness analysis of the PR and IMT methods in COVID-19 patients; and third, patients with all viral types of pneumonia will be educated beforehand about the potential benefits or harmful effects of engaging in physical activity and exercise programs that include IMT, so that they can take an informed decision.

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Acknowledgments

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Contributors

VM conceived of the study design, obtained ethical approval and funding. VM, GCJ and LVFO developed the main study intervention. JCC, GFBC, MCO, MMC, MEM and LPC contributed to study design. VM and GCJ wrote the first draft of the paper, and RB, ANC, IOS, AGBL, DBS and LPC revised the first draft. The final manuscript was reviewed by all the authors. All authors read and approved the final manuscript.

Competing Interests

None declared.

FIGURE LEGENDS

Figure 1: Flow chart

Figure 2: Template of recommended content for the schedule of enrolment, interventions, and assessments

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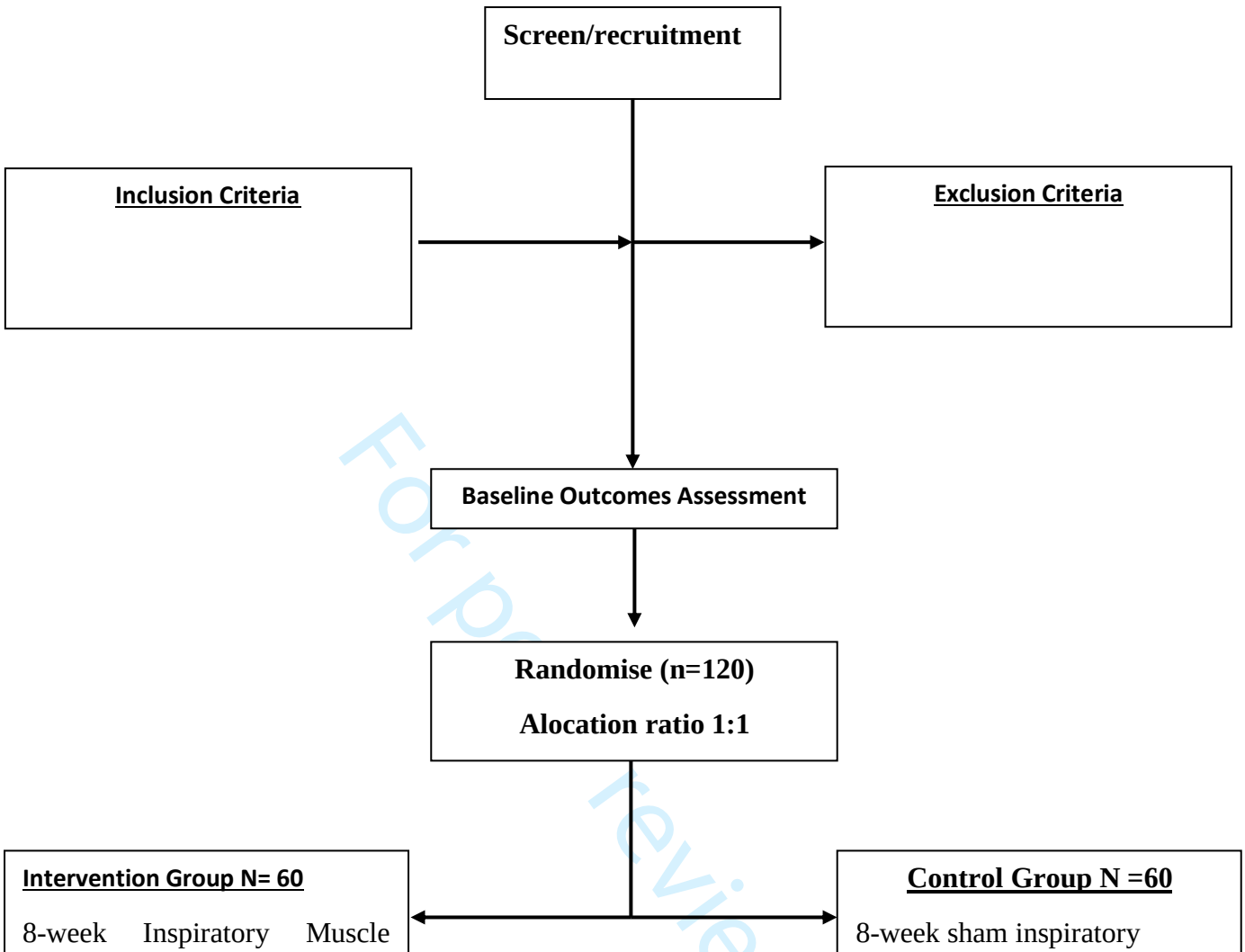

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Figure 2. **T**emplate of recommended content for the schedule of enrolment, interventions, and assessments.

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			
TIMEPOINT**	***-t_1***	**0**	***t_1*** ***Baseline***	***t_2*** **8 Weeks**	***t3 16 weeks***	***t_x*** ***6 Months***
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
[IMT + Pulmonary Rehabilitation]			←	—		
[Sham IMT + Pulmonary Rehabilitation]			←	—		
ASSESSMENTS:						
[Clinical and Demographic Carachteristics]	X					
[Cardiopulmonary Exercise Testing]			X	X	X	
[mMRC]			X	X	X	
[EQ 5D 5L]			X	X	X	
HADS			X	X	X	
FSS			X	X	X	
Inspiratory Muscle Strength			X	X	X	
Inspiratory Muscle Endurance			X	X	X	
Cost-utility analysis						X

Legends: IMT = inspiratory muscle training; mMRC = modified medical research council dyspnea scale; HADS = hospital anxiety and depression scale; FSS = fatigue severity scale.

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	6
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	ok
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	ok

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

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