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Pursuing Reduction in Fatigue After COVID-19 via Exercise and Rehabilitation (PREFACER): a protocol for a randomised feasibility trial

Nicole Billias ,[1,2,3,4] Dimitra V Pouliopoulou ,[3,4] Arden Lawson,[1,2] Victoria D'Alessandro,[3,4] Dianne M Bryant,[3,4] Sue Peters,[3,4] Alison B Rushton ,[3,4] Erin Miller,[3] Laura Brunton,[3] Shannon McGuire,[2] Michael Nicholson,[2] Trevor B Birmingham,[3,4] Joy C MacDermid ,[1,2,3,4] Kieran L Quinn ,[5] Fahad Razak,[5] Susie Goulding,[6] Panagis Galiatsatos,[7] Emily Saunders,[3] Jacquelyn Marsh,[1,3,4] Tiago V Pereira,[8] Pavlos Bobos [1,3,4]

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For numbered affiliations see end of article.

Correspondence to
Nicole Billias; nbillias@uwo.ca

ABSTRACT

Introduction Over 777 million COVID-19 infections have occurred globally, with data suggesting that 10%–20% of those infected develop Long COVID. Fatigue is one of the most common and disabling symptoms of Long COVID. We aim to assess the feasibility and safety of a new, remotely delivered, multimodal rehabilitation intervention, paced to prevent post-exertional malaise (PEM), to support the conduct of a future, definitive randomised trial.

Methods and analysis We will conduct a randomised, two-arm feasibility trial (COVIDEx intervention vs usual care). Sixty participants with Long COVID will be recruited and randomised prior to giving informed consent under a modified Zelen design using 1:1 allocation with random permuted blocks via central randomisation to receive either the COVIDEx intervention or usual care. The 50-minute, remotely delivered, COVIDEx intervention will occur twice weekly for 8 weeks. All participants will wear a non-invasive device throughout their entire study participation, to track heart rate, blood oxygen saturation, steps, sleep and monitor PEM. The primary feasibility objectives will be recruitment rates, intervention fidelity, adherence, acceptability (intervention and design), retention, blinding success and outcome completeness. Secondary objectives will include refined estimates for the standard deviation and correlation between baseline and follow-up measurements of fatigue. Feasibility and clinical outcomes will be collected at baseline, 4, 8, 12 and 24 weeks. Qualitative interviews with participants and physiotherapists will explore intervention acceptability and barriers/facilitators.

Ethics and dissemination Ethical approval for this study was obtained by the Western University Health Sciences Research Ethics Board (REB# 123902). Dissemination plans include sharing of trial findings at conferences and through open access publications and patient/community channels.

Trial registration number NCT06156176

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The modified Zelen design minimises disappointment/contamination effects and reflects real-world adherence.
⇒ Qualitative interviews with an intersectional equity lens examine feasibility, acceptability and adherence.
⇒ Using ecological momentary assessment (EMA) enables real-time measurement of post-exertional malaise (PEM) and fatigue by reducing recall bias.
⇒ This feasibility trial is not powered to evaluate effectiveness, and its small sample size may limit the generalisability of the findings in different populations and/or settings.

INTRODUCTION

Background and rationale

Long COVID, also known as post-COVID-19 condition (PCC), is characterised by persistent symptoms that significantly impact health, functioning and quality of life months after acute SARS-CoV-2 infection.[1] The World Health Organization (WHO) defines PCC as symptoms that begin or continue at least 3 months after infection, last for at least 2 months and cannot be explained by alternative diagnoses.[2 3] Despite growing awareness, Long COVID remains poorly understood, highly heterogeneous and controversial, with debates over its pathophysiology, risk factors and optimal treatment approaches.[3 4]

A conservative global estimate suggests at least 65 million cases of Long COVID, but the true burden is likely higher due to underreporting and undocumented infections.[3] Prevalence estimates range from

10–30% in non-hospitalised cases, 50–70% in hospitalised cases and 10–12% in vaccinated individuals.[3] This substantial burden translates into a significant public health crisis, with major economic and healthcare implications, including reduced workforce participation, increased healthcare utilisation and high disability rates.[5]

Among the most disabling and defining symptoms of Long COVID is fatigue, which is present in over 50% of cases.[6] A subset of Long COVID patients may experience post-exertional malaise (PEM), which is a pathological condition that may share mechanisms with other post-viral syndromes such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[3] PEM is a distinguishing feature of Long COVID in which physical or cognitive exertion leads to symptom exacerbation, often lasting days or weeks.[7]

Despite widespread recognition of the burden of Long COVID, current treatment strategies remain fragmented, unproven and largely based on expert consensus rather than high-quality evidence.[6] Rehabilitation guidelines are primarily derived from observational studies or adapted from interventions designed for other conditions, such as chronic fatigue syndrome or post-ICU rehabilitation.[1] Existing trials of rehabilitation interventions for Long COVID suffer from major limitations, including small sample sizes, lack of control groups, high risk in performance and detection bias, and heterogeneity in intervention protocols.[6 8–10]

To address these critical gaps, we have developed COVIDEx, a novel, remotely delivered, multimodal rehabilitation programme specifically designed for Long COVID fatigue. COVIDEx integrates patient-centred strategies, including energy conservation techniques, cognitive behavioural approaches and structured pacing principles, to mitigate PEM risks while improving functional capacity.[11] The intervention was informed by existing rehabilitation frameworks, which have shown promise in managing chronic fatigue syndromes.[12] Our hypothesis is that a structured, individualised rehabilitation approach will improve fatigue and quality of life in Long COVID patients while minimising the risk of symptom exacerbation such as PEM.

Study purpose

This single-centre feasibility, two-arm randomised trial aims to evaluate the feasibility and safety of COVIDEx in Long COVID patients with fatigue. The study will assess key feasibility metrics, including recruitment rates, adherence, intervention fidelity, acceptability, retention and outcome completeness.

Objectives

The primary objectives of this feasibility trial are to assess recruitment rates, adherence (showing up to rehabilitation sessions and follow-ups), intervention fidelity, acceptability (programme and modified Zelen design), participant retention, blinding success and outcome completeness (see table 1).

Table 1 Study objectives and outcomes table

Objective	Outcome(s)
Recruitment rate	► Recruitment rate (primary)
Adherence	► Retention rate (primary) ► Burden of completing all assessments and sessions for patients and physiotherapists (secondary)
Acceptability of the modified Zelen design	► Modified Zelen design acceptability, qualitative (primary)
Participant retention	► Retention rate (primary)
Blinding success	► Blinding success rate (secondary)
Outcome completeness	► Burden of completing all assessments and sessions for patients and physiotherapists (secondary) ► Clinical outcomes
Intervention fidelity	► Intervention fidelity (primary)
Acceptability of the COVIDEx intervention	► Patient perceptions and intervention acceptability, qualitative (secondary)
Usefulness of the intervention	► Patient perceptions and intervention acceptability, qualitative (secondary)

The secondary objective of this study is to obtain reliable estimates of the standard deviation and correlation between the baseline and follow-up measurements of the primary outcome (fatigue), which will inform calculation of the sample size of the definitive trial. In exploratory Bayesian analyses, we plan to calculate the posterior predictive probability of trial success to guide decisions on the viability of advancing with a definitive trial.

Trial design

We will conduct a single-centre, randomised two-arm modified Zelen[13] feasibility trial. We will use a 1:1 randomisation ratio, in which patients will be randomly assigned to receive either the COVIDEx intervention or usual care. We chose a modified Zelen design to enhance participation and minimise disappointment effects and biases (ie, contamination bias).[14–16] Participants will be informed that they are participating in an observational study following the natural progression of Long COVID and costs associated with standard treatments. At the end of their study participation, participants will be debriefed about the trial design and asked to provide consent for the use of their data.

METHODS AND ANALYSIS

Participants, interventions and outcomes

Study setting

This study will take place at Parkwood Institute in London, Ontario, Canada. Participants will be identified and recruited from the community and St. Joseph's Post-Acute COVID-19 outpatient programme at Parkwood Institute. Once the clinician and research personnel have determined eligibility, they will log into the web-based computer-generated randomisation system on a hospital-network-based Research Electronic Data Capture (REDCap) database. The randomisation scheme will be constructed using varying, permuted blocks, stratified by sex and hospitalised status (1=hospitalised, 0=otherwise). In alignment with the modified Zelen design's unique approach, all participants will be randomised before obtaining their informed consent. Additionally, five to eight physiotherapists will be recruited as study participants. They will be trained to deliver the COVIDEx intervention, conduct physical assessments with patient participants and participate in one-on-one interviews with a research team member to evaluate feasibility.

Consent process

All patient participants will be informed that they are part of an observational study designed to follow the natural progression of Long COVID and to evaluate the costs associated with standard post-COVID-19 treatments. This includes both the COVIDEx and usual care groups. Blinding patients to the presence of the experimental group will mitigate the effects of feeling disappointed, frustrated or discouraged about being assigned usual care. This is important given that the study is also assessing fatigue, a subjective, patient-reported outcome measure. This approach can also reduce the likelihood that participants in the usual care group begin self-motivated programmes trying to mimic the intervention. Upon completion of the study, both groups will attend a disclosure call where the randomised nature of the study will be revealed, the rationale for this deception/treatment delay will be provided and full informed consent to use their data for the randomised controlled trial (RCT) will be sought. The deception disclosure calls for participants will occur over the phone. A research coordinator or assistant will telephone each participant on completion of the participant's study procedures and disclose the deception to participants. Usual care patients will then be offered the COVIDEx intervention. The treatment period will be 8 weeks, with 2 COVIDEx sessions per week. Figure 1 outlines the participant timeline.

Eligibility Criteria

Inclusion criteria

A research coordinator will determine patient eligibility after a physician has completed a history and physical examination. To ensure patient participant safety, screening questions will be used to assess functional ability and Long COVID symptom management. This will help determine if people can safely participate in the study. Physiotherapist participants will be recruited from St. Joseph's Health Care London. To participate in the trial, participants must meet the following inclusion criteria:

Patient participants

- Adults of at least 18 years of age.
- Able to provide informed consent.
- Can speak and understand English.
- Documented history of SARS-CoV-2 infection (positive PCR/antigen test during acute illness or clinical diagnosis by physician during or after the acute illness).
- Fatigue symptoms within 3 months of COVID-19 infection, lasting at least 2 months.
- Fatigue symptoms cannot be explained by an alternative diagnosis.
- Fatigue symptoms may be new onset following initial recovery from an acute COVID-19 infection or persist from the initial illness.
- Fatigue symptoms may have an episodic nature, fluctuate or relapse over time.
- Minimal functional capability: able to walk 10–15 minutes and be recovered within 30–60 minutes or without significant PEM.
- Has applicable technology to access Microsoft Teams and Webex (ie, computer, laptop or tablet).

To ensure the above criteria are met, participants will only be included in the study if they meet all eligibility criteria more than 12 weeks from the onset of their acute COVID-19 symptoms.

Physiotherapist participants

- Adults aged 18 or older.
- Able to provide informed consent.
- Can speak and understand English.
- Currently registered/licensed with a provincial or territorial regulatory physiotherapy college in Canada.

Physiotherapists will lead 16 total COVIDEx sessions (twice weekly for 8 weeks), complete five 30-second sit to stand assessments for a patient participant and complete a one-on-one virtual interview with a member of the research team at the end of the study procedures.

Exclusion criteria

Patient participants

- Active SARS-CoV-2 infection.
- Pre-existing physical, cognitive and/or mental health conditions that make exercise contraindicated, consent unattainable or that cause symptoms similar to those seen in post COVID-19 (ie., major neurocognitive disorder, schizophrenia, chronic fatigue syndrome) that could affect data.
- Inability to follow study procedures.
- Pregnant and/or breastfeeding.

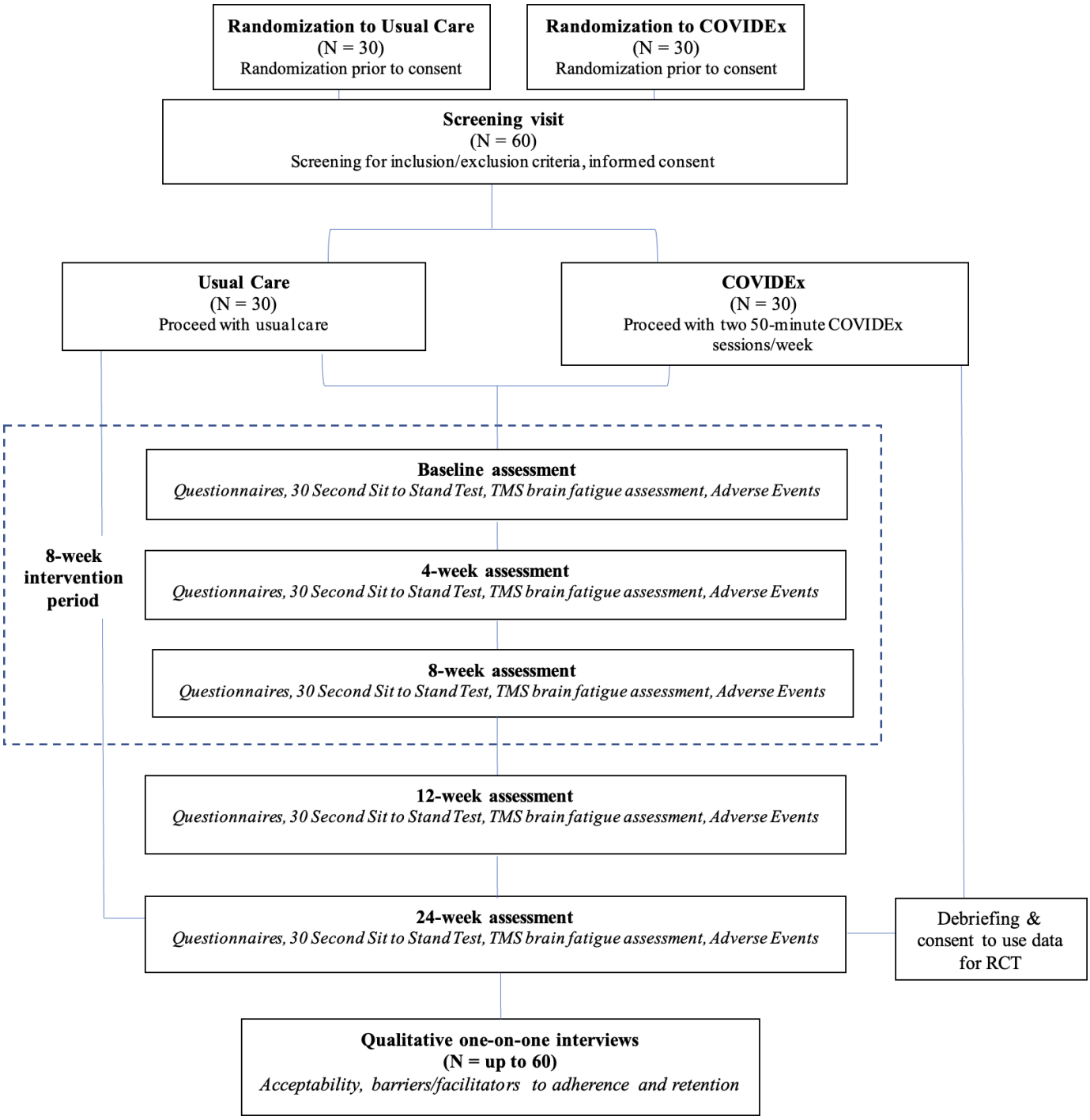

Figure 1 Schematic of participant timeline. RCT, randomised controlled trial; TMS, transcranial magnetic stimulation.

- Received investigational agents as part of a separate study within 30 days of the screening visit.
- Has any type of metal bodily implant in head or heart (ie, pins, plates and pacemakers).
- Current participation in other studies related to COVID-19, exercise and/or fatigue interventions OR participation within 30 days of the screening visit.

As this is a feasibility trial for Long COVID, participants will not be excluded if they are receiving other care or treatment options, as there is no established usual care for the condition. However, participants undergoing or starting other care for Long COVID will be asked to promptly notify the research team and provide details, which will be recorded throughout their study participation.

Interventions

COVIDEx physical therapy rehabilitation programme

The COVIDEx intervention will be delivered by trained instructors and comprises of two 50-minute sessions each week (48 hours apart) for 8 weeks. It is designed to be delivered virtually via a hospital-based Microsoft Teams account in groups of 6 patients, to eliminate

travel requirements for the study. The components of the programme are the following: (1) warm-up (1 minute), (2) cardiovascular training (5 minutes), (3) rest (3 minutes), (4) balance training (5 minutes), (5) breathing training (3 minutes), (6) cognitive training (5 minutes), (7) strengthening training (5 minutes) and (8) stretching (10 minutes). The COVIDEx intervention will be paced to prevent PEM in participants. This pacing strategy includes taking subjective measurements of exertion (using the Borg RPE 0–10 scale) from participants throughout the sessions, monitoring and safely cuing participants, and ensuring adequate rest in between components of the intervention. To improve adherence, participants will be reminded of upcoming sessions and attendance will be monitored by a research coordinator or assistant. Participants will be instructed to promptly report any side effects or challenges they experience throughout the study to the research team. The team will work with the participant to assess if the intervention needs to be discontinued or modified.

Usual care

The control group will receive usual care, which does not include physiotherapy. Current available treatment options for people with Long COVID include immunomodulatory therapies (eg, pegylated alpha-interferon),[17] antivirals,[18] monoclonal antibodies,[19] anti-inflammatory agents (eg, colchicine),[20] anti-platelet agents (eg, aspirin),[21] fluvoxamine[22] and traditional Chinese medicine.[23]

Any concomitant treatments (including start and end dates) will be recorded for all participants. This information will be summarised descriptively to document the range of treatments received in both groups and to inform the design of the definitive trial.

Outcomes

Outcomes will be collected at baseline, 4, 8, 12 and 24 weeks after randomisation. Outcomes include feasibility measures and clinical outcomes, including assessment of cortical excitability via transcranial magnetic stimulation (TMS). Qualitative one-on-one interviews with patients and physiotherapists will explore the acceptability of the intervention and barriers/facilitators to intervention adherence and study retention. Both COVIDEx and control group participants will be asked to participate in the interviews. The study team will only collect data from the usual care participants for the duration of the trial. If the usual care participants choose to participate in the COVIDEx intervention after deception is revealed, no data will be collected.

Primary and secondary outcomes

We will use the 'traffic light' approach to assess feasibility outcomes relative to the criteria for progression to the definitive RCT[24] (see table 5). Table 1 outlines all study objectives and outcomes.

Primary feasibility outcomes

Recruitment

Number of screened patients who are eligible, the proportion of eligible patients who consent, number of patients enrolled per month, reasons for non-enrolment.

Intervention fidelity

Proportion of participants who meet the acceptable level of intervention fidelity (>80%). A fidelity checklist will be used to assess feasibility that includes adherence (delivery of each key component of the intervention—yes/no, number of sessions completed), dosage (amount of intervention delivered, overall duration of sessions), quality of intervention delivery (how well the intervention is delivered by physiotherapists), and participant acceptability (extent to which participants in the intervention group found the intervention useful). The fidelity checklist will be completed at the end of each session by a research assistant, who will be attending all COVIDEx sessions to ensure standardisation and consistency.

Retention

Proportion of missed assessments and incomplete outcome measures data, and proportion of participants who withdraw from the trial.

Modified Zelen design acceptability

Proportion of patients in the usual care group who provide consent to include their data in the RCT following the disclosure visit.

Secondary feasibility outcome measures

Blinding success rate

Success rate of blinding of the patients and outcome assessors will be evaluated with the James Blinding Index (JBI) scale. The JBI is a continuous value such that 0<= JBI ≤1. If the index is 1, all responses are incorrect, and complete blinding is inferred, although this may indicate unblinding in the opposite direction (eg, opposite guessing). If the index is 0, all responses are correct, and complete unblinding is inferred. If the index is 0.5, then half of the guesses are correct and half of the guesses are incorrect, inferring random guessing. Unblinding may be claimed if the upper limit of the two-sided confidence interval is <0.5. The JBI has yet to be specifically validated in Long COVID and other chronic fatigue populations; however, its established reliability and validity in other clinical trial settings[25] support its use in our trial. The JBI will be evaluated at the end of the trial (24 weeks).

Qualitative methodology (participant perceptions)

Upon completion of the study protocol, we will ask all participants and treating physiotherapists to take part in a one-on-one, semi-structured qualitative interview to understand their perceptions of acceptability of the intervention and their experiences with the modified Zelen design. Understanding the acceptability of the intervention will inform the extent to which it is feasible in a real-world setting. In addition, participants will be asked to

share their perspectives around study participation and completion to optimise our recruitment and retention strategies for the definitive trial. This qualitative methodology section was written in accordance with the *Consolidated Criteria for Reporting Qualitative Research* (COREQ) 2007 statement.[26]

The interviews will use an interpretive description approach[27] to focus on clinically meaningful findings that inform our understanding of the acceptability of the intervention, perceived benefits, barriers/facilitators to adherence and implementation challenges. Additionally, they will implement an intersectional[28] equity lens by exploring whether gender, income, educational factors and gender roles act as potential mediators of acceptability, barriers/facilitators and adherence. We will conduct interviews with all 60 participants (continuing until thematic saturation is reached), as well as with treating physiotherapists who participated in the trial. Interviews will be virtual, last approximately 60 min and be recorded using a hospital-based Microsoft Teams account. The interviewers will be provided with a semi-structured interview guide. The audio recordings will be transcribed using Trint Transcription Software, and the transcriptions will be analysed using NVivo. Data analysis will be iterative: data will be analysed as it is collected using both inductive and deductive coding. The study team will use coding (two separate coders to ensure inter-rater reliability), thematic analysis and comparison to identify patterns and themes. Reflexivity will be maintained by the research team throughout the qualitative component.

Clinical outcomes

Clinical outcomes[29] will only be assessed for completion and will not be used to compare the effectiveness of interventions across groups. The burden of outcome measure completeness will be assessed using the following indicators: proportion of missing visits, missing outcomes/data and reasons for missingness, assessed separately for each outcome measure. Participant demographics (age, sex, gender, occupational status, body mass index) will be obtained at baseline. Health history will be collected at enrolment and updated at baseline and weeks 4, 8, 12 and 24. The PROMIS-Fatigue scale, with established psychometric properties across many populations,[30–32] will be used to measure participants' fatigue levels on a 5-point Likert scale at baseline and at weeks 4, 8, 12 and 24. Pain levels will be measured using the Visual Analogue Scale (VAS-Pain),[33] at baseline, weeks 4, 8, 12 and 24. The following scales will also be administered at the same time points: Post COVID-19 Functional Status,[34 35] Borg Scale of Perceived Exertion (RPE),[36 37] Global Rating of Change Scale (GroC),[38] DePaul Symptom Questionnaire (DSQ),[39 40] Hospital Anxiety and Depression Scale (HADS),[41 42] EuroQoL-5D,[43 44] adverse events questionnaires, including the DSQ-PEM.[45]

Additionally, the 30 second sit-to-stand assessment[46 47] will be used to measure leg strength and endurance. TMS will be used to assess brain function. Both of these outcomes will also be administered at baseline, and 4, 8, 12 and 24 weeks.

Transcranial magnetic stimulation (TMS)

We will assess potential changes in corticomotor excitability and motor evoked potential (MEP) amplitudes in response to the COVIDEx rehabilitation intervention, using single pulse measurements and a recruitment curve.[48] The resting motor threshold (RMT) stimulator percentages will be administered in a randomised order (rather than in an ordered, sequential manner) to prevent biases, adaptation and fatigue and ensure that corticomotor excitability is accurately captured. TMS will be administered in the Gray Centre at Parkwood Institute. Procedures will be in accordance with published TMS safety standards.[49] The participant's dominant arm will be placed in a relaxed position on the armrest of the chair or on a pillow. MEPs of the dominant hand first dorsal interosseous muscle will be elicited using a figure-of-eight coil with a Magstim Rapid II TMS system. Neuronavigation using BrainSight and the template brain will ensure the coil position remains stable throughout the TMS protocol. RMT will be assessed, defined as the lowest TMS intensity that evokes MEPs of at least 50 microVolts peak-to-peak amplitude in 5/10 stimulations. The TMS sessions will last approximately 1 to 1.5 hours each.

Ecological momentary assessment (EMA) data collection

To continuously assess PEM and fatigue in this trial,[11 29] an EMA design will be used to ask participants how they are feeling at random time-points after participating in the COVIDEx sessions (up to 24 weeks follow-up). For comparison, participants in the usual care group will also be administered the EMA questions. The EMA questions are based on the DePaul Symptom Questionnaire-SF,[50] as a screening tool.[40]

Participants will be asked to download the web mobile application, which will administer the questions at random time-points, two times a day, for 24 weeks. Notifications will pop up on participants' mobile device(s), and participants will select 'yes' or 'no' to whatever random question pops up. Participants may encounter one open-ended question where they will type their response about how they are feeling.

To also assess PEM and fatigue, and for safety purposes, we will collect and analyse participants' heart rate, blood oxygen levels, steps activity (number of steps per day) and sleep. This data will also be accumulated using the web mobile application. Participants in both the usual care and COVIDEx groups will be wearing a smart watch as much as possible for the full 24-week study period. The smart watch will be provided by the study team at no cost to the participant. The participant may also use their own personal smart watch to collect these measures; however, this is a choice and if the participant is uncomfortable with using their own personal device, one can be provided to them. Participants may be required to input basic profile information on the smart watch, such as

email, age, height, weight and/or gender to personalise the tracking features.

For data privacy and security purposes, the smart watches will be password protected when not in use. Additionally, all data will be deleted from the smart watch once the data has been uploaded to the web mobile application and the participant has completed all study procedures. EMA data will be collected for 24 weeks once the participant signs the consent form and agrees to participate in the study. Once all data collection is complete, the data will be downloaded from the web mobile application and saved to the secure hospital network.

Management of post-exertional malaise (PEM)

A subgroup of patients with Long COVID may indicate that they experience PEM on the pre-screening and demographic questionnaires. PEM is defined as new or worsening symptoms (such as difficulty thinking, problems sleeping, sore throat, headaches, feeling dizzy or severe tiredness) up to 48 hours after a physical or mental activity that would not have caused a problem before COVID-19 infection and subsequent post-COVID-19 fatigue.[51–53] Symptoms of PEM can last for days, weeks or months.[53] We will address PEM in the trial by the following:

a. *Pacing the COVIDEx session to reduce over-exertion.* A pacing strategy and protocol may reduce exacerbation of PEM for those with Long COVID.[54] Pacing will entail frequently gathering subjective measurements of intensity from participants, as well as ensuring that all components of the session (ie., cardiovascular, strength training) have adequate rest and recovery in between periods of more intense activity. Participants will inform the physiotherapist or exercise instructor of their resting heart rate and blood oxygen levels before each session and after each component of the session, which will help determine the rehabilitation intensity and pacing.
b. *Monitoring correlated measures for blood lactate levels in participants.* People with Long COVID may experience skeletal muscle abnormalities, such as mitochondrial and endothelial dysfunction, and a change to primarily anaerobic metabolism and glycolytic muscle fibres.[52 55] These changes can reduce movement capacity and potentially trigger PEM.[52] Potential causes for these skeletal muscle abnormalities include deconditioning, local tissue hypoxia, autoimmunity, electrophysiological changes and central fatigue (neurological alterations).[52] Monitoring correlated measures for blood lactate enables examination of these metabolic responses (ie, mitochondrial dysfunction, reduced tissue oxygenation) in people with Long COVID,[56 57] which could help prevent the onset of PEM by ensuring participants do not exceed a threshold that could induce PEM. Specifically, our objective of monitoring correlated measures for blood lactate is for safety purposes to prevent overreaching in participants with Long COVID. All COVIDEx participants, throughout the COVIDEx sessions, will use a smart watch to monitor correlated measures for their blood lactate levels, specifically heart rate[58] and blood oxygen.[59] Steps activity and sleep will also be monitored to track physical activity and sleep disturbances. This device is required to be worn by participants as often as possible over the 24-week study period, but especially during each COVIDEx session. Participants will be asked to inform the physiotherapist or exercise professional of their blood oxygen levels and heart rate at various time points throughout the COVIDEx intervention, so the instructor can gauge intensity and modify rehabilitation intensity as needed. The instructor will have the lactate range table (see table 2 below) on hand to ensure participants are within the safe and functional overreaching zones and will approximate this based on participants' blood oxygen levels. If oxygen saturation falls below 92%, participants will be advised not to take part in (or discontinue) the session, and this will be recorded promptly.

Table 2 indicates altered lactate level zones proposed for people with Long COVID, adapted from concepts in applied sports settings.[56] The ranges are used here to contextualise thresholds of exertion, with the goal of distinguishing between safe activity levels and those that may increase the risk of overexertion or symptom exacerbation (PEM). The objective of monitoring

Table 2 Lactate level zones—Long COVID

Safe zone	Functional overreaching	Overreaching	Danger zone
0.5–0.99 mmol/L	1–1.99 mmol/L	2–2.99 mmol/L	≥3 mmol/L
Rest>volume and intensity of exercise/stimuli>*max exertion*.			

Table 3 Lactate level zones—regular

Safe zone	Functional overreaching	Overreaching	Danger zone
0.5–1.99 mmol/L	2–2.99 mmol/L	3–4 mmol/L	>4.01 mmol/L
Rest>volume and intensity of exercise/stimuli>*max exertion*.			

correlated measures for blood lactate is to keep participants within the safe and functional overreaching zones.

For comparison, table 3 indicates lactate level zones for healthy individuals, who have a larger safe zone.[56] A healthy blood lactate level at rest is around 0.5–1 mmol/L.

Sample size

The requirement of 30 patients per group is consistent with general guidelines for feasibility and pilot RCTs[60] and is supported by recent suggestions for pilot RCT sample size calculations based on our adopted 'traffic light' approach.[24] Thirty participants per treatment group provides a sufficient sample size to reliably estimate the standard deviation and the correlation between baseline and follow-up fatigue measurements.[24 60 61]

Recruitment

Patient participants

People with Long COVID (n=60) will be recruited from the Post-Acute COVID-19 Program at Parkwood Institute and the community (ie, community-dwelling people not referred into the Post-Acute COVID-19 Program). Potential participants will first be pre-screened for eligibility and sent to their treating physician for approval. After a member of the circle of care obtains permission from the patient, a member of the study team will approach the patient to explain the study. Using a modified Zelen design, participants will be assigned on a 1:1 basis to the novel rehabilitation programme (COVIDEx) or usual care. Thirty participants will be randomised to each treatment group.

Community advertisements (posters, online and in-person) will also be used to recruit and inform potential participants about the study. Posters will be displayed at Parkwood Institute, Elborn College and the Western Interdisciplinary Research Building. The study will also be promoted through various media and social media outlets, and online research platforms. The recruitment poster will be posted online via Facebook (specifically, the Facebook pages Wortley Villager Magazine, Old South Community Board and Old South, Wortley Village and Highlands Neighbourhoods). Interested participants can reach out to Parkwood staff via contact information on the advertisements.

Physiotherapists will lead 16 total COVIDEx sessions (twice-weekly for 8 weeks), complete five 30 second sit to stand assessments for a patient participant and complete a one-on-one virtual interview with a member of the research team at the end of the study procedures (24 weeks). The physiotherapist participant will be trained in how to administer the COVIDEx sessions and paperwork for the 30 second sit to stand assessment. Physiotherapist participants are eligible for a one-on-one qualitative interview with a research team member (to explore intervention acceptability and barriers/facilitators) if they assisted with administering at least one scale/test/questionnaire or led at least one COVIDEx session for at least one patient participant as part of the PREFACER study.

Assignment of interventions

Allocation

Sequence generation

Once the participant has been deemed eligible, the research coordinator will log into the web-based computer-generated randomisation system on a hospital-network-based REDCap database. The randomisation scheme will be constructed by REDCap and will use varying, permuted block sizes (4, 6 or 8), stratified by sex and hospitalised status (1=hospitalised, 0=otherwise).

Allocation concealment mechanism

The allocation sequence will be implemented using the hospital-based REDCap database, which will conceal the sequence until participants are assigned to their respective treatment arms.

Implementation

A research coordinator or assistant will screen and enrol eligible participants. The REDCap database will generate the allocation sequence and assign participants to interventions.

Blinding

Participants in both groups will be blinded to the intervention via the modified Zelen design (ie, will be informed that they are participating in an observational study following the natural progression of Long COVID and costs associated with standard treatments, then later debriefed). Outcome assessors (ie, select research assistants from the study team and some physiotherapist participants) will be blind to group allocation, which will ensure that conversations, encouragement and measurements conducted by the outcome assessor will not influence outcomes. Participants will be instructed not to reveal or discuss the intervention with the outcome assessor. The data analyst will be blinded by receiving de-identified data. Unblinding will only take place during a closed meeting with the trial steering committee where safety concerns are raised by the data, or if a patient requires medical attention with the study team.

Data collection, management and analysis

Data collection methods

Data collection will be completed by a research coordinator and assistant, following the schedule of events (see table 4). The research team, under the guidance of the principal investigator, will undergo protocol training to ensure familiarity with all study procedures. This training will include assigning and signing off on study-related responsibilities. Physiotherapists delivering the COVIDEx intervention will receive training and a standardised manual to ensure consistent delivery of the intervention across participants. Data collection forms will be stored both on paper and in a secure, hospital-based REDCap database. Paper records will be kept in a locked cabinet

Table 4 Schedule of events table

Procedures	Enrolment	Baseline (Week 0)	Week 4	Week 8	Week 12	Week 24
Eligibility screen	X					
Consent	X					
Intervention allocation		X				
Functional screening	X					
Debriefing and data consent						X
Interventions						
COVIDEx		X	X	X		
Usual care		X	X	X		
Assessments						
Health history		X	X	X	X	X
Demographics		X				
PROMIS-Fatigue		X	X	X	X	X
VAS-Pain		X	X	X	X	X
DSQ-SF		X	X	X	X	X
DSQ-PEM-SF		X	X	X	X	X
HADS		X	X	X	X	X
EQ-5D		X	X	X	X	X
PC-19-FS		X	X	X	X	X
30CST		X	X	X	X	X
Borg RPE		X	X	X	X	X
GRoC		X	X	X	X	X
TMS		X	X	X	X	X
Gender, pain, expectations		X	X	X	X	X
EMA		X	X	X	X	X
Adverse events		X	X	X	X	X
JBI						X

30CST, 30 Second Sit to Stand Test; DSQ-PEM-SF, DePaul Symptom Questionnaire – Post-Exertional Malaise – Short Form; DSQ-SF, DePaul Symptom Questionnaire – Short Form; EMA, ecological momentary assessment; EQ-5D, EuroQol – 5 Dimension; GroC, Global Rating of Change; HADS, Hospital Anxiety and Depression Scale; JBI, James Blinding Index; PC-19-FS, Post-COVID-19 Functional Status; RPE, Borg Rating of Perceived Exertion; TMS, transcranial magnetic stimulation; VAS, Visual Analog Scale.

within a secured office at Parkwood Institute, with access limited to authorised personnel.

To promote participant retention and follow-up, contact and emergency contact information will be collected. Additionally, the study team will ensure flexibility with assessments and scheduling, as well as multiple reminder calls for upcoming sessions and assessments. As this is a feasibility trial, our primary and secondary outcomes will collect data regarding participants who discontinue or deviate from intervention protocols.

Data management

The study team will handle data according to the Data Management Plan as outlined below:

- No identifiable information (eg, name, phone number and email) about participants will be kept with the research data.
- All identifiable information about participants will be replaced with a code. A master list linking the code and identifiable information will be kept separate from the research data on an encrypted, password-protected computer at Parkwood Institute.
- Participant research data and records will be maintained in a secure location at Parkwood Institute. Only authorised individuals will have access to it.
- Research data collected for the study will be de-identified and held in a database. The study database will be maintained on Lawson REDCap on a hospital server (a server at St. Joseph's Health Care London).
- The research data and records will be kept for approximately 15 years, per institutional policy.

The study's biostatistician will be the only external recipient of de-identified data, as they are responsible for performing the data analysis. A data sharing agreement

has been initiated and will be in place prior to sharing any de-identified data off-site. All data will be shared off-site via a secure file transfer.

Information collected during the study will be stored on paper and maintained at the site in individual participant files. The data will then be entered directly into our REDCap database. The data entered will consist only of the participant ID, answers to study questionnaires and data from assessments.

Participant identity will always be kept confidential, including when study results are published, except where disclosure is required by law. A study team member may access participant personal medical records for health information, such as: information about participant post-COVID-19 fatigue, past medical history and current medications. Any information obtained during this study will be kept confidential. Study records that leave the study site will not contain participant names.

Statistical methods

The feasibility RCT data will be collected, and one analysis will be carried out after the last participant's final follow-up visit. The feasibility outcomes will be analysed after the last participant completes the 6-month follow-up visit.

We will assess outcomes for the entire sample but will also conduct a separate evaluation according to sex (males and females separately).[62] To arrive at estimates of the standard deviations and correlations between the baseline and follow-up scores for the PROMIS-Fatigue scale, we will estimate the primary outcome's variance-covariance structure and convert it into a correlation matrix. The latter will be used to refine our sample size estimation for the definitive trial via Monte Carlo simulations. We will summarise continuous variables with mean (standard deviation) or median (interquartile range). Categorical variables will be presented as numbers (percentages). Proportions will be estimated with the Clopper-Pearson exact 95% confidence interval.

Bayesian posterior predictive probability of success (PPoS)

We will calculate Bayesian posterior predictive probabilities of success (PPoS). A PPoS is the probability of claiming that COVIDEx is superior to usual care, given the evidence from the pilot trial participants and an increased sample size beyond the originally planned sample size (eg, 40 or 50 additional participants). These analyses will be exploratory, but if the PPoS are sufficiently high, they will increase our confidence in the intervention and better justify conducting a larger definitive trial.[63]

Bayesian model for the PPoS

We will use an analysis of covariance (ANCOVA) model, with the treatment group (1=COVIDEx, 0=usual care) and baseline PROMIS-F scores as independent variables.[64] The dependent variable will be the PROMIS-F scores at the follow-up (6 months). We will use non-informative (vague) prior distributions for all parameters and will construct the predictive distribution via Markov chain Monte Carlo using Gibbs sampling.

In our model, when the true mean difference (MD) between COVIDEx and usual care is negative, it indicates superiority. Thus, when the MD<0, it implies that participants allocated to the COVIDEx group were associated with lower fatigue scores after treatment than those receiving usual care. The probability of superiority will be defined as the posterior probability that MD<0 is greater than 97.5%, or Pr(MD<0) >0.975, which is approximately equivalent to a two-sided frequentist P value of 0.05.[65]

To calculate the PPoS, we will generate 10 000 simulations of size $60+N_2$ and will estimate the proportion of simulations showing superiority. N_2 represents the hypothetical number of additional participants to be recruited to the trial assuming a 1:1 randomisation ratio (ie, the predictive sample). The magnitude of N_2 will be defined later, based on the refined parameters from the feasibility trial. Bayesian analyses will be run with 3 chains, each with 10 000 iterations (totaling 30 000 iterations)—after a burn-in of 10 000 simulations. Since graphical convergence checks are not feasible for each simulation, we will assess convergence in all simulations using the Brooks-Gelman–Rubin R statistic. Specifically, the R statistic will be calculated for each simulation, with values greater than 1.1 indicating non-convergence. In such cases, the results will be discarded and replaced by a new simulation. Results will be summarised using posterior medians with 95% credible intervals (95% CrI). Credible intervals will be based on the 2.5th and 97.5th percentiles of the posterior distributions. We will use Stata (version 18, StataCorp, Texas, USA)[66] and OpenBUGS (MRC Biostatistics Unit, Cambridge, UK) in all analyses.

Monitoring

Data monitoring

A trial steering committee will be responsible for final decisions regarding the conduct of the study and decisions regarding premature termination of the trial. The steering committee will consist of Drs Bobos, Peters, Nicholson, Bryant, Galiatsatos, Razak, Goulding (patient partner) and Quinn. A Data and Safety Monitoring Board (DSMB) that is independent of trial investigators will be established for the definitive trial. Adverse events (including treatment-emergent adverse events) will be closely monitored after a participant has provided consent and has formally enrolled in the trial and will be gathered until study close out. All serious adverse events occurring after enrolment will be reviewed by the DSMB and reported to the ethics review board. Bi-annual open (all participants without separation by group) and closed reports (separation by blinded group) of recruitment, retention, completeness and representativeness will be provided to the DSMB for review and recommendations will be sent back to the trial steering committee.

Following guidelines,[24] criteria to progress from feasibility to definitive RCT are listed in table 5. No interim analyses will be conducted. Each primary feasibility

Table 5 Progression criteria to assess feasibility for a phase III confirmatory trial[24]

Feasibility outcome	Green zone: Proceed	Amber zone: Proceed with changes	Amber zone: Cut-off	Red zone: Do not proceed
Recruitment (avg/month)	6–8	4		<2
Intervention fidelity	≥80%	60%	60%	<40%
Adherence	≥80%	60%	60%	<40%
Acceptability of the rehabilitation programme	≥80%	60%	60%	<40%
Retention	≥85%	<85% and >75%	75%	<65%
Modified Zelen acceptability	≥90%	<90% and >85%	85%	<75%
Blinding success	≥80%	60%	60%	<40%
Outcome completeness	≥80%	60%	60%	<40%

outcome measure will be assessed separately, and the overall progression will be determined by the worst-performing criterion. If all signals fall into the green zone, we will proceed to the definitive trial without changes. If none of the signals falls into the red zone but at least one falls into the amber zone, the design of the trial procedures will be amended before proceeding to the definitive trial. If at least one signal falls into the red zone, we will not proceed to the definitive trial. Feasibility outcomes that include a qualitative component (intervention fidelity, acceptability and modified Zelen acceptability) will be assessed and incorporated into the criteria.

Harms

Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs): A TEAE is any undesirable or unintended medical event that happens to a participant (whether the event is related to the COVIDEx intervention or not). A SAE is any adverse event that leads to death, is life-threatening, requires hospitalisation (or prolongation of existing hospitalisation), and/or leads to persistent or significant disability or incapacity. The research team will collect, document and promptly report all TEAEs and SAEs to the Principal Investigator and Qualified Investigator. The trial steering committee will carefully assess all TEAEs and SAEs and will monitor all study dropouts due to TEAEs and SAEs during the trial.

Auditing

Authorised representatives of the following organisations may at any time, audit participant records, research chart and identifiable medical/clinical records at the study site to check that the information collected for the study is both correct and follows proper laws and guidelines:

- Representatives of the Western University Health Sciences Research Ethics Board (an independent committee) that oversee the ethical conduct of this study to help protect the rights and welfare of study participants.
- This institution and affiliated sites to oversee the conduct of research at this location.
- The Quality Assurance and Education Officers from Lawson Health Research Institute (Lawson) may audit this research study for quality assurance purposes.

Patient and public involvement

Patients with Long COVID were involved in the development and initial testing of the COVIDEx prototype. The COVIDEx programme and prototype were informed by the lead physiotherapist (McGuire, co-author) and initial feedback from 28 patients attending the Post-Acute COVID-19 outpatient clinic at Parkwood Institute. This feedback helped refine the COVIDEx programme for the trial.

Ethics and dissemination

Research ethics approval

Ethical approval for this study was obtained by the Western University Health Sciences Research Ethics Board (REB# 123902). Institutional approval from Lawson Health Research Institute and St. Joseph's Health Care London has been obtained. Additionally, the database in which participant information will be stored, REDCap, has been approved by Lawson Health Research Institute prior to entering any patient participant information.

This trial protocol was reported in accordance with *Standard Protocol Items for Randomised Trials* (SPIRIT) 2025 statement for protocols of randomised clinical trials.[67]

Protocol amendments

Any proposed protocol modifications will be reviewed by the Principal Investigator and research team and submitted to the Western University Health Sciences Research Ethics Board for ethical approval prior to implementation. If required by the ethics board, protocol modifications will be communicated to current and past study participants, as well as other relevant stakeholders.

Consent

A member of the research team (ie, research coordinator or assistant) will obtain informed consent from potential trial participants. The team member will provide the consent form to the participant and allow the participant to have as much time as needed to review it and ask any questions. If the participant decides to participate in the study, the research team member will thoroughly review the consent form with them and address any remaining questions the participant may have. Finally, the participant and study team member will sign the consent form.

Confidentiality

The study team will follow the Data Management Plan (see subsection Data management under Methods: Data collection, management and analysis) to ensure participant confidentiality before, during and after the trial. Identifiable information (eg, names, contact details) will not be stored with research data and will be replaced with coded identifiers. A master list linking codes to personal information will be securely stored on an encrypted, password-protected computer at Parkwood Institute. Research data will be de-identified, entered into a secure Lawson REDCap database, and maintained on protected hospital servers and Amazon Web Services servers in Ontario. Access to data will be limited to authorised personnel, and all data shared externally with the study's biostatistician will be de-identified and transferred securely under a data sharing agreement. Participant identity will remain confidential in all publications, except when required by law. Personal medical records may be accessed by the study team for relevant health information but will remain confidential, and study records leaving the site will not contain participant names.

Access to data

The Principal Investigator will have access to the final trial dataset and the study's biostatistician will be the only external recipient of de-identified study data (which has been approved by the Western University Health Sciences Research Ethics Board). A data sharing agreement between the biostatistician and St. Joseph's Health Care London has been initiated and will be in place prior to sharing any de-identified data off-site, which has also been approved by the ethics board. All data will be shared off-site via a secure file transfer.

Ancillary and post-trial care

Participants will be informed in the consent form that the study may uncover unexpected findings about their health. If this occurs, the researchers will consult medical experts, share the findings with the participant and help in arranging appropriate follow-up care. Participants will also be advised that any injuries resulting from study participation will receive medical attention at no cost. Additionally, they will be informed that they can request a copy of the COVIDEx manual, although a physical therapist will not be available to deliver the intervention to them post-trial.

Dissemination policy

The study team will disseminate trial findings to clinicians and researchers at major national and international conferences, through publication in open access peer-reviewed journals, and patient/community channels.

Author affiliations
[1]Lawson Research Institute, London, Ontario, Canada
[2]St. Joseph's Health Care London, London, Ontario, Canada
[3]School of Physical Therapy, Western University, London, Ontario, Canada
[4]Bone and Joint Institute, Western University, London, Ontario, Canada
[5]Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[6]COVID Long-Haulers Support Group Canada, Oakville, Ontario, Canada
[7]School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA
[8]Nuffield Department of Population Health, University of Oxford, Oxford, UK

Contributors PB (guarantor) conceptualised the trial and is responsible for its implementation, conduct, analysis, interpretation and publication. DMB assisted with designing the clinical and methodological aspects of the trial. ABR designed the trial's patient engagement strategy. SP was responsible for designing the trial's TMS methodology. JCM was responsible for designing the trial's qualitative methodology. TVP provided medical biostatistical experience to the research team. AL assists with the study in a research coordinator role, provides administrative support and assisted with drafting the article. NB, DVP, VD and ES are involved in all aspects of the trial in trainee roles and assisted with drafting the article. KLQ, FR, PG and SG oversee the trial's safety. JM, EM and SM oversee the clinical aspects of the COVIDEx programme. LB oversees the link between the trial's research conduct and clinical implementation. TBB helped design the trial's mobility assessments and will take primary responsibility for conducting them. All authors reviewed and approved the protocol and article.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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ORCID iDs
Nicole Billias https://orcid.org/0009-0009-8479-3530
Dimitra V Pouliopoulou https://orcid.org/0009-0000-0730-0610
Alison B Rushton https://orcid.org/0000-0001-8114-7669
Joy C MacDermid https://orcid.org/0000-0001-9311-7379
Kieran L Quinn https://orcid.org/0000-0002-1681-5170
Pavlos Bobos https://orcid.org/0000-0002-5098-4840

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