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Optimized tDCS for fibromyalgia – targeting the endogenous pain control system: A randomized, double-blind, factorial clinical trial protocol

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ABSTRACT

Introduction

Fibromyalgia is a common debilitating condition with limited therapeutic options. Medications have low efficacy and are often associated with adverse effects. Given that FM is associated with a defective endogenous pain control system and central sensitization, combining interventions such as transcranial direct current stimulation (tDCS) and aerobic exercise to modulate pain-processing circuits may enhance pain control.

Methods and analysis

A prospective, randomized (1:1:1:1), placebo-controlled, double-blind, factorial clinical trial will test the hypothesis that optimized tDCS (16 anodal tDCS sessions combined with aerobic exercise) can restore of the pain endogenous control system. Participants with FM (n=148) will undergo a conditioning exercise period and be randomly allocated to one of four groups: (1) active tDCS and aerobic exercise (2) sham tDCS and aerobic exercise, (3) active tDCS and non-aerobic exercise, or (4) sham tDCS and non-aerobic exercise. Pain inhibitory activity will be assessed using conditioned pain modulation (CPM) and temporal slow pain summation (TSPS) – primary outcomes. Secondary outcomes will include the following assessments: Transcranial Magnetic Stimulation (TMS) and electroencephalography (EEG) as cortical markers of pain inhibitory control and thalamocortical circuits; secondary clinical outcomes on pain, fibromyalgia impact, quality of life, sleep and depression. Finally, the relationship between the two main mechanistic targets in this study – CPM and TSPS – and changes in secondary clinical outcomes will be tested. The change in the primary efficacy endpoint, CPM and TSPS, from baseline to week 4 of stimulation will be tested with a mixed linear model and adjusted for important demographic variables.

Ethics and dissemination

This study obeys the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Partners Healthcare under the protocol number 2017P002524. Informed consent will be obtained from participants. Study findings will be reported in conferences and peer-reviewed journal publications.

Trial registration
NCT03371225

Strengths and Limitations

- A sham-controlled, powered clinical trial on a novel low-cost therapy for fibromyalgia.
- Endogenous pain system biomarkers will help reveal the mechanisms of fibromyalgia as well as the interventions.
- This study will inform us on the number of sessions needed to induce significant changes in neuroplasticity reflected in the above mentioned markers.
- The secondary outcomes of this study will evaluate the suitability of the proposed biomarkers to predict treatment response.
- Exclusion of patients with increased risk during exercise may limit the generalizability of the findings.

INTRODUCTION

Fibromyalgia (FM) affects about 2% of the world population (1) and is associated with poor quality of life mainly due to pain, fatigue, sleep disturbances, functional limitations and cognitive impairments (2). Current treatments for this challenging complex condition for FM lead to an average annual cost of $5,945 in insurance claims per FM patient, more than twice the amount of a typical beneficiary (3). The treatment of choice is a multimodal approach that includes self-management strategies (4), but there is a large gap between supply and demand as access to such therapies is limited. Consequently, many FM patients rely on pharmaceuticals such as nonsteroidal anti-inflammatory drugs, antidepressants, and/or anticonvulsants, which usually do not provide enough symptom relief and are frequently associated with adverse effects (5). Therefore, there is an urgent need for the development of novel and targeted treatments with fewer side-effects.

Rationale and gap

Accumulating evidence (6-9) shows that disturbances in the endogenous pain control system lead to chronic pain. Several neurophysiological (10-16) and neuroimaging (17-21) studies showed altered pain processing mechanisms in FM; therefore, therapies that target and modulate the neural circuits involved in pain control are essential to treat FM characteristic chronic widespread pain. Different ways to potentially modulate these circuits include exercise- which has a known evidence-based therapeutic effect on pain in FM (22), and non-invasive neuromodulation techniques such as transcranial direct current stimulation (tDCS)- which demonstrably improve several chronic pain conditions (23-28). Despite its investigated benefits to treat different pain conditions (typically targeting the primary motor cortex (M1)), tDCS effects in FM have been mixed (29-32). Yet tDCS can be easily coupled to other therapies due to its low-cost and portability (33), and such combinations have been superior to either of the therapies alone in other disorders (34-36). We have shown in a pilot study with 45 FM subjects that combining exercise and tDCS for FM leads to a significant pain decrease that also shows a different neural signature as compared to each therapy alone (tDCS or exercises) (37). In this initial study, however, the endogenous pain inhibitory system was not assessed.

Given the extensive data showing that (i) FM has a defective endogenous pain inhibitory system (10-16) and (ii) exercises (38-40) and TDCS lead to modulation of this system (31, 41, 42), we then hypothesized that these two neuromodulatory techniques can help restore the endogenous pain inhibitory system in FM. Neurophysiological and clinical assessments including Electroencephalography (EEG), Transcranial Magnetic Stimulation (TMS), quantitative sensory testing and questionnaires for pain and quality of life can provide important data to understand how the endogenous pain inhibitory system is then modulated by these two interventions.

Research question and hypothesis

We therefore aimed to test whether in subjects with FM 16 sessions of M1 anodal tDCS combined with aerobic exercise decrease temporal slow pain summation (TSPS) and increase conditioned pain modulation (CPM) responses compared to each intervention alone and to sham when assessed on the last day of intervention. We hypothesize that this optimized tDCS plus aerobic exercise technique will lead to a stronger engagement of the endogenous pain regulatory system, which will ultimately lead to increased pain regulation in patients with FM.

Objectives

Primary objective:

- To evaluate the effects of 4 weeks of tDCS plus aerobic exercise on the endogenous pain regulatory system (assessed by CPM) and central sensitization (assessed by TSPS) compared to either interventions alone and to no intervention.

Secondary objectives:

- To determine the effect of these interventions on cortical markers of inhibitory control that are also altered in FM, such as intracortical inhibition assessed by TMS, and changes in thalamocortical dysrhythmia (TCD) and event related desynchronization (ERD) assessed by EEG;
- To assess whether engagement of the two main targets tested in this study (TSPS and CPM) are associated with the secondary clinical outcomes (i.e. changes in pain outcomes: Brief Pain Inventory, Revised Fibromyalgia Impact Questionnaire);
- To assess EEG changes across groups and their suitability as potential markers of TCD normalization;
- To determine the number of sessions needed to induce significant changes in markers of the endogenous pain inhibitory system and central sensitization (CPM and TSPS) and cortical changes (paired pulse TMS and EEG).

METHODS AND ANALYSIS

Trial Design

This is a single center 4-arm factorial RCT. Participants will be randomized using a random blocked randomization sequence generated by a computer software. We used a 1:1:1:1 allocation ratio to active or sham tDCS combined with aerobic (AE) or non-aerobic exercise (nAE) on the first day of the conditioning exercise program. The staff member performing randomization will not be involved in the trial otherwise. Sequentially numbered sealed envelopes will maintain allocation concealment. Investigators providing assessments will be blinded to tDCS but not exercise. Assessors of primary and secondary outcomes (and participants) will be blinded to group allocation. (See Figure 1 for group allocation).

Study setting

This is a single-site study, all procedures will be conducted at the Neuromodulation Center, Spaulding Rehabilitation Hospital.

Eligibility Criteria

We will use broad-based recruitment strategies, including online advertisements, flyers, clinician referrals, etc. All eligible participants must fulfill the inclusion criteria and have none of the exclusion criteria listed in **Table 1.**

Table 1: Inclusion and exclusion criteria

Inclusion criteria:

1) Age range 18-65 years,

2) Diagnosis of FM pain according to the ACR 2010 criteria (existing pain for more than 6 months with an average of at least 4 on a 0-10 VAS scale) without other comorbid chronic pain diagnosis,

3) Pain resistant to common analgesics and medications for chronic pain such as Tylenol, Aspirin, Ibuprofen, Soma, Parafon Forte DCS, Zanaflex, and Codeine,

4) Must have the ability to feel sensation by Von-Frey fiber on the forearm,

5) Able to provide informed consent to participate in the study.

Exclusion criteria:

1) Clinically significant or unstable medical or psychiatric disorder,

2) History of substance abuse within the past 6 months as self-reported (if subject reports a history of substance abuse, we will confirm using DSM V criteria),

3) Previous significant neurological history (e.g., traumatic brain injury), resulting in neurological deficits, such as cognitive or motor deficits, as self-reported,

4) Previous neurosurgical procedure with craniotomy,

5) Severe depression (with a score of >30 on the Beck Depression Inventory),

6) Pregnancy - as the safety of tDCS in pregnant population (and children) has not been assessed (though the risk is non-significant), we will exclude pregnant women (and children). Women of child-bearing age will be required to take a urine pregnancy test during the screening process and in every week of stimulation),

7) Current opiate use in large doses (more than 30mg of oxycodone/hydrocodone or 7.5mg of hydromorphone (Dilaudid) or equivalent),

8) Patients will be excluded when they have increased risk for exercise defined as (i) not fulfilling the American College Of Sports Medicine (ACSM) criteria (i.e. risk of cardiovascular complication (43)) and in this case not cleared by a licensed physician.

As part of the eligibility criteria, participants will perform a pre-training visit to evaluate if they are comfortable with walking on the treadmill at a self-selected speed at their baseline heart rate (HR) for 30 minutes. Only subjects comfortable with this task will be randomized. If the subject is unable to walk for 30 minutes on the treadmill or reports discomfort or any side-effects precluding physical exercise (e.g., excessive muscle soreness), they will be screened out. Also, a demographic survey will be taken during the consent visit.

Intervention

Exercise

Conditioning exercise program: 6 exercise sessions are divided in 3 days per week over 2 weeks. Duration of sessions will start with 10 minutes and increase gradually, ending with a 30-minute session on the last day. The AE group will walk briskly at 60-70% of their maximum Heart Rate (HR) and the nAE group will walk within 5% of their baseline HR. If a participant on the AE group is unable to progress beyond 15 min at 60-70% HR max over the initial 2 weeks, they will be screened out of the study. After the conditioning exercise program, subjects will continue with the intervention part of the protocol. Participants will complete aerobic or non-aerobic exercise 3 times a week on nonconsecutive days over 4 weeks.

Aerobic exercise (AE): Participants will undergo moderate intensity AE on a treadmill over 30 minutes (American Heart Association recommendation for adults). HR will be monitored throughout the entire procedure by a sensor. The investigator will sequentially increase the treadmill speed by 0.1 mph every 5 seconds, until the participant reaches 60-70% of age-predicted maximal heart rate (HRmax), following the formula HRmax = 208 − (0.7 * age), as this has been found safe in various conditions (22, 44-48). AE intensity will be modulated based on the participant's HRmax throughout the session. If the HRmax exceeds 70%, the investigator will decrease treadmill speed by 0.1 mph every 5 seconds until returning to the 60-70% HRmax target. If HRmax reaches 80% or the subject shows any signs of discomfort, the session will be stopped.

Non-aerobic exercise (nAE): Participants will walk on the treadmill for 30 minutes with a workload intensity within 5% baseline HR, as we used this method in our preliminary study(37).

As recommended by ACSM guidelines for AE in FM patients , the participant will be questioned regarding any respiratory or cardiovascular symptoms on each visit before starting the exercise; we will monitor pain and fatigue levels after the first 5, 15 and 25 minutes of exercise using a numeric pain scale (43). Additionally, to evaluate adverse effects during AE or nAE training, we will record any musculoskeletal symptoms such as pain, muscle strain, muscle soreness, fatigue, dizziness and shortness of breath.

Transcranial Direct Current Stimulation (tDCS)

A 1x1 Low-intensity DC Stimulator, the Soterix Medical 1x1 tDCS-Clinical Trial, will be used with codes corresponding to active or sham stimulation, allowing a double-blinded procedure. Participants will receive 16 tDCS sessions over 4 weeks of treatment. Weeks 1 and 2 will begin with 5 consecutive days of tDCS followed by Weeks 3 and 4 with 3 alternating days of tDCS. The exercise and the tDCS will be performed simultaneously as explained on Figure 2.

Active (anodal) tDCS: During active tDCS, a 2mA constant current will be delivered for 20 minutes through rubber electrodes encased in 35 cm^2 saline-soaked sponges. The anode will be placed over the left primary motor cortex (M1) and the cathode over the contralateral supraorbital area. M1 will be localized using the 10/20 International EEG System (C3 – adapted by measuring 5 cm below the vertex), a reliable method for tDCS(23).

Sham tDCS: We will use the same montage and parameters as active tDCS, but the active current will be applied for 30 seconds in the beginning and at the end of the procedure to simulate the same sensations of

the current ramping as in active stimulation (49). Using 30 seconds of ramping is reliable for blinding (50) and less than 3 minutes of tDCS induces no cortical excitability effects (49).

A TDCS adverse events questionnaire will be administered after each stimulation session. Subjects will be instructed not to use other methods of electrical stimulation during the trial.

Outcomes

Evaluation of Endogenous Pain Inhibition System (Primary Outcomes)
During the CPM and TSPS protocols, heat pulses will be generated by a TSA-II Stimulator (Medoc Advanced Medical Systems, Ramat Yishai, Israel) delivered to the right proximal volar forearm using a 30mm x 30mm embedded heat pain (HP) thermode. A minimum interval of 10 minutes between the two assessments will be respected.

Conditioned pain modulation (CPM) evaluates the ability to inhibit pain. When a pain test stimulus is given together with a conditioning pain stimulus, the test stimulus is perceived as less painful than when it was given alone (51). We will follow the adapted protocol suggested by Granot et al., 2008(52) and Nirl et al., 2011(53). We will first determine the pain-60 test temperature (which is the temperature that induces pain sensation at a magnitude of 60 on a 60-100 numerical pain scale (NPS)) by applying a Peltier thermode (Medoc Advanced Medical Systems, Ramat Yishai, Israel) on the right forearm and delivering three short heat stimuli (43, 44, and 45 °C), each lasting 7 seconds (starting from the time the stimulus intensity reaches the destination temperature). Subjects will be asked to rate the level of pain intensity using a numerical pain scale (NPS) ranging from 0 = "no pain'' to 100 = "the worst pain imaginable''. If the first temperature of 43 °C is considered too painful (>60/100), we will stop the series and will provide additional stimuli at lower temperatures of 41 and 42 °C. If the three temperatures (43, 44, and 45 °C) are unable to achieve pain-60, we will deliver additional stimuli at 46, 47, and 48 °C until reaching the desired pain level of 60/100; in the unlikely event that none of those temperatures elicits pain-60, we will consider it to be 48°C. On determining the pain-60 temperature, we will administer the test stimulus at that temperature for 30s, and subjects will be asked to rate their pain intensity at 10, 20 and 30s after the thermode reaches the pain-60 temperature (mean scores of the three pain ratings will be calculated). Five minutes after delivering the test stimulus, the conditioning stimulus will be applied: the subject's left hand will be immersed for 30s in a water bath set at 10-12°C. Then the same pain-60 temperature will be applied to the right forearm (left hand will still be immersed) for 30s and the subject will again be asked to rate their pain intensity 3 times after the thermode reaches the pain-60 temperature: at 10, 20 and 30s (mean scores of the three pain ratings will be calculated). CPM response will be calculated as the difference between the average of pain ratings from the test stimulus minus the average of pain ratings during the conditioned stimulus.

Temporal slow pain summation (TSPS) represents summation of C fiber mediated pain, assesses central sensitivity, and is used to probe pain processing abnormalities in several chronic pain disorders (54, 55). Subjects will be trained to identify pain-60 test temperature (see CPM protocol above) and we will follow the adapted protocol suggested by Staud et al., 2014 (56) in which the HP-thermode was programmed to deliver pulses with rise/fall of 1-2s, depending on subject's pain-60 level, from adapting temperatures to peak temperatures, with a plateau of 0.7s. They will receive 1 train of 15 repetitive heat stimuli at 0.4 Hz, which (being suitable to elicit TSPS in most subjects) allows the rating of individual pain stimuli and is

unlikely to induce peripheral sensitization (57). TSPS will be calculated as the difference between heat pain rating after the 1st and 15th stimuli.

Evaluation of cortical markers of inhibitory control

Transcranial magnetic stimulation (TMS)

To assess tDCS and AE effects we will measure the excitability of pain-related pathways using TMS markers. TMS assessments will be similar to our previous study (58). Single pulse TMS will be performed to acquire resting motor threshold (rMT) and motor evoked potentials (MEPs); paired pulse technique will measure short interval cortical inhibition (SICI) and intracortical facilitation (ICF). We will use Magstim Rapid^2 device with a figure-of-eight magnetic stimulator coil placed on the right and left M1 (for all assessments) and will record surface electromyogram (EMG) from the contralateral first dorsal interosseous (FDI) muscle. TMS data will be recorded and stored in a computer for off-line analysis.

1. *Resting motor threshold (rMT)*: Initially we will investigate rMT following the technique described by Rossini and colleagues, where rMT is defined as the lowest stimulus intensity to evoke a MEP of 100 μV in 3/5 trials in the relaxed muscle (59).

2. *Motor evoked potential*: We will initially adjust TMS machine output intensity to achieve a baseline MEP of 1 mV peak-to-peak amplitude before the intervention. Stimulation intensity will be kept constant for each subject throughout the evaluation sessions. We will record 10 MEPs for each assessment and average their peak-to-peak amplitudes and areas-under the-curve.

3. *Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF):* We will use paired pulse testing with a subthreshold conditioning stimulus (80% rMT) followed by a suprathreshold test stimulus of 120 % of the motor threshold. Interstimulus intervals will be 2ms for SICI and 10ms for ICF. Ten randomized stimuli will be applied at each interval and the percentage of inhibition or facilitation for each interstimulus interval before and after treatment will be calculated. The paired pulse MEP intensity will be the machine output intensity eliciting 1 mV peak-to-peak amplitude that day – not the baseline MEP intensity used for single pulse testing. If we cannot obtain rMT, we will not perform MEPs or paired pulse.

Electroencephalography (EEG)

EEG will take place over approximately 45 min: 25 minutes of participant and software preparation, 10 minutes of EEG recording divided into a resting EEG condition (5 minutes with eyes open, 5 minutes with eyes closed), and a task-related condition (8 minutes). Participants will be asked to relax in the resting condition; the investigator will ensure they do not fall asleep.

The task-related condition will include movement observation (MO), movement imagery (MI) and movement execution (ME). This will be recorded by connecting the Net Station software (for EGI) with E-Prime®. The entire task-related condition part will consist of 60 trials, with 20 trials for each of MO, MI and ME in a randomized order (60, 61). Each trial will involve initial fixation (on a cross on a screen), followed by a visual cue stating the task to be performed ("imagine" and "clench"), and a video will automatically play for observation. During each MO trial, the participant will view a video of a right hand

clenching; during the MI task the participant will be asked to imagine clenching her/his right hand once, and during the ME task the subject will be asked to clench her/his right hand once. There will be a 4 second rest period between each trial. The purpose of the task-related condition is to evaluate ERD that reflects the motor cortex activation (62).

We will record the EEG in a standardized way (63) using the 64-channel EGI system (EGI, Eugene, United States of America). The EEG will be recorded with a band-pass filter of 0.3– 200 Hz and digitized at the sampling rate of 250 Hz (64) by connecting the Net Station software (for EGI) with E-Prime®. On acquiring the EEG data, the EEGs will be inspected and artifacts will be cleaned manually. We will use EEGLAB and analysis of EEG data will include a power analysis of the power bands in the resting EEG portion - delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz) bands - fast fourier transformation (FFT), ICA decomposition, ERD responses of the three different motor tasks, functional connectivity measures and topographical analysis. The analysis will compare groups at baseline, during the stimulation period, on the last day of the intervention and at the 3-months follow-up.

Secondary Clinical Outcomes

The following secondary outcomes will be assessed: average pain intensity as assessed by Modified Brief Pain Inventory (BPI); Revised Fibromyalgia Impact Questionnaire (FIQ-R); quality of life assessed by Quality of Life Scale (QoLS), Patient Reported Outcomes Measurement Information System (PROMIS); Pittsburgh Sleep Quality Index (PSQI) and Beck Depression Inventory (BDI).

Timeline

This trial has 25 visits divided into 4 components (consent and pre-training walking, conditioning exercise program, intervention and follow-up). To increase adherence to protocol, we will adjust the calendar of sessions according to the subject's availability. See figure 2 below.

Study Sample

Our target population is individuals with FM according to the ACR 2010 criteria. We plan to enroll 148 subjects divided into 4 groups (n=37/group).

Sample Size Calculation

We used the information from trials measuring the effects of tDCS and aerobic exercise on CPM and TSPS according to different scenarios to do this sample size calculation (See Table 2 below):

- In Scenario I we considered the effects of tDCS on CPM in patients with chronic pain: this resulted in an effect size (ES) of 0.79.
- In Scenario II we evaluated the effect of tDCS on CPM in healthy volunteers: this resulted in a pooled ES of 1.02.
- In Scenario III we evaluated the effect of exercise on CPM in chronic pain and this resulted in an ES of 0.78.

Study	Population	Intervention	Effect Size
Scenario I: TDCS effect on CPM in chronic pain			
Ribeiro et al. 2017 (65)	40 women with chronic pain undergoing hallux valgus surgery	Active vs. sham tDCS.	Cohen's d = 0.79

Scenario II: TDCS effect on CPM in healthy volunteers			
Braulio et al. 2018 (66)	48 healthy males	Active-tDCS + remifentatnil vs. sham-tDCS + remifentanil	Cohen's d = 0.98
Flood et al. 2017 (67)	12 healthy males	Active HD-tDCS vs sham HD-tDCS	Cohen's d = 1.38
Flood et al. 2016 (68)	30 healthy males	Active vs. sham tDCS	Cohen's d = 0.89
Silva et al. 2015 (69)	20 healthy males	Active tDCS + melatonin vs. placebo + sham-tDCS	Cohen's d = 0.67
Pooled effect size			1.02
Scenario III: Exercise effect on CPM in chronic pain			
Meeus et al. 2015 (70)	16 rheumatoid arthritis	Exercise pre and post	Cohen's d = 0.78

Table 2: Effect size in 3 scenarios.

Based on this analysis, we decided upon a conservative approach and chose the lowest ES; thus, we used an ES of 0.78. In addition, it is important to underscore that we expect that the combination of tDCS + aerobic exercise will have a higher effect than each intervention alone (tDCS, exercise, or placebo). Additionally, in this current proposal the dosage of tDCS is higher than the studies we used to calculate the sample size (see Tables 2 and 3).

We assumed a type I error of 5% (alpha), and made a sensitivity analysis with a type 2 error (beta) of 10%, 15% and 20% (therefore a power of 90%, 85%, and 80%). We used a t-test for 2 independent means and considered dropout rates of 20% and 15%. See Table 3 below:

	Alpha	**ES**	**Dropout rate**	**Final total sample size (4 groups)**
Power of 80%	5%	0.78	15%	124
Power of 85%	5%	0.78	15%	142
Power of 90%	5%	0.78	15%	165
Power of 80%	5%	0.78	20%	130
Power of 85%	5%	0.78	20%	148
Power of 90%	5%	0.78	20%	172

Table 3: Two-tailed analyses

Although most studies used a power of 80% and a dropout rate of 10 to 15% (22, 29, 71-76) we chose a dropout rate of 20% and power of 85% as to be more conservative and also account for unexpected factors.

Data analysis

All data collected will be kept in a secured and password protected database, accessible only to IRB trained and approved study staff. All analyses will be performed as intention-to-treat in which all randomized subjects who receive at least one intervention session will be included. We will conduct sensitivity analyses and test different models of handling missing data: Last Observation Carried Forward and Multiple Imputation. The change in the primary efficacy endpoints, CPM and TSPS, from baseline to week 4, will be tested with a mixed linear regression model. This model will be adjusted for important demographic variables (e.g., gender) and baseline clinical parameters where appropriate. All tests will be two-sided (alpha level 0.05).

We will initially test our main hypothesis that active tDCS+AE increases CPM and decreases TSPS more than sham tDCS+nAE. If the effect is significant, we will then test differences between the active tDCS+AE group versus the two interventions alone. We will run a secondary mixed linear model to estimate the rate of change over time (using the secondary endpoints added in this model - Week 2 and follow-up), and also include the interaction term (treatment*time) to detect whether treatment effect changes differently over time. If the interaction is not significant, we will then test whether there is a main effect of time that is independent of treatment level (interaction will be removed from the model). We will adjust this model for important covariates such as age, gender, pain levels (NPS), and other baseline clinical outcomes where appropriate. For secondary clinical variables with significant effects, we will test whether they moderate the interventions' effects on our mechanistic (TMS and EEG) outcomes, thereby gaining additional mechanistic insights. To complete our analysis, we will apply a path analysis (77) to CPM and TSPS to determine if endogenous pain modulation changes (indexed by CPM and TSPS) associated with active tDCS+AE is related to direct effects versus indirect effects through secondary outcome improvements. We propose that a direct effect of active tDCS and AE on the endogenous pain inhibitory system can be inferred if the treatment effect cannot be explained by changes in psychological or functional outcomes.
An independent monitoring committee (IMC) will review data on recruitment, adherence and safety; meetings will occur annually, after enrollment of 25% of the target sample or in case of reports of any serious adverse events. NIH will also perform annual site monitoring visits.

Patient and public involvement
Patients and public were not involved in the design of this study.

Ethics and dissemination
This protocol was approved by the IRB at the Partners Human Research Committee (Protocol approval number: 2017P002524). All requirements regarding the welfare, rights, and privacy of human subjects protection were fulfilled. The risks of this clinical trials were considered to be minimal and are addressed in the protocol and consent form. Informed consent will be obtained from all participants before any study procedures by the Principal Investigator or co-investigators. Trial registration number: NCT03371225. For a complete list of trial registration dataset and protocol version history please refer to Supplementary Files 1 and 2.

The study findings will be reported in conferences and in peer-reviewed journal publications.

Contributors: LCB and EUK are joint first authors and with FF conceptualized the paper. PGM, LC and AEG wrote the Abstract. LCB, EUK, LC, MEG wrote the Introduction. ACR, CBP, IMT, EUK, LCB, ME, KPB, PGM, DD and YY wrote Methods and Analysis. ACR, IGM and YY prepared the figures. FF, ME, WC and HH provided critical review.

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Competing Interest
The authors declare no competing interests with this research.

Ethics Approval
This study obeys the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Partners Healthcare under the protocol number 2017P002524

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement: Upon completion of the trial and after publication of the primary manuscript, we plan to provide access to the de-identified dataset following the guidelines of our institution (Spaulding Rehabilitation Hospital/Partners Healthcare and Harvard Medical School).

REFERENCES

1. Wolfe F, Brähler E, Hinz A, Häuser W. Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population. Arthritis care & research. 2013;65(5):777-85.
2. Verbunt JA, Pernot DH, Smeets RJ. Disability and quality of life in patients with fibromyalgia. Health and Quality of Life Outcomes. 2008;6(1):8.
3. Robinson RL, Birnbaum HG, Morley MA, Sisitsky T, Greenberg PE, Claxton AJ. Economic cost and epidemiological characteristics of patients with fibromyalgia claims. The Journal of rheumatology. 2003;30(6):1318-25.
4. Adams N, Sim J. Rehabilitation approaches in fibromyalgia. Disability and Rehabilitation. 2005;27(12):711-23.
5. Häuser W, Walitt B, Fitzcharles M-A, Sommer C. Review of pharmacological therapies in fibromyalgia syndrome. Arthritis research & therapy. 2014;16(1):201.
6. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annual review of neuroscience. 1984;7(1):309-38.
7. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. The Journal of clinical investigation. 2010;120(11):3779-87.
8. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. Current opinion in supportive and palliative care. 2014;8(2):143.
9. Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. Expert review of neurotherapeutics. 2012;12(5):577-85.
10. de la Coba P, Bruehl S, Moreno-Padilla M, Reyes del Paso GA. Responses to slowly repeated evoked pain stimuli in fibromyalgia patients: evidence of enhanced pain sensitization. Pain Medicine. 2017;18(9):1778-86.
11. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. 2005;114(1-2):295-302.
12. Mhalla A, de Andrade DC, Baudic S, Perrot S, Bouhassira D. Alteration of cortical excitability in patients with fibromyalgia. Pain. 2010;149(3):495-500.
13. Gibson S, Littlejohn G, Gorman M, Helme R, Granges G. Altered heat pain thresholds and cerebral event-related potentials following painful CO2 laser stimulation in subjects with fibromyalgia syndrome. Pain. 1994;58(2):185-93.
14. Stevens A, Batra A, Kötter I, Bartels M, Schwarz J. Both pain and EEG response to cold pressor stimulation occurs faster in fibromyalgia patients than in control subjects. Psychiatry research. 2000;97(2-3):237-47.
15. Cardinal TM, Antunes LC, Brietzke AP, Parizotti CS, Carvalho F, De Souza A, et al. Differential neuroplastic changes in fibromyalgia and depression indexed by up-regulation of motor cortex inhibition and disinhibition of the descending pain system: an exploratory study. Frontiers in human neuroscience. 2019;13.
16. Deitos A, Soldatelli MD, Dussán-Sarria JA, Souza A, da Silva Torres IL, Fregni F, et al. Novel Insights of Effects of Pregabalin on Neural Mechanisms of Intracortical Disinhibition in Physiopathology of Fibromyalgia: An Explanatory, Randomized, Double-Blind Crossover Study. Frontiers in human neuroscience. 2018;12.
17. Pujol J, López-Solà M, Ortiz H, Vilanova JC, Harrison BJ, Yücel M, et al. Mapping brain response to pain in fibromyalgia patients using temporal analysis of FMRI. PloS one. 2009;4(4):e5224.
18. Williams DA, Gracely RH. Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia. Arthritis research & therapy. 2007;8(6):224.

19. Burgmer M, Pogatzki-Zahn E, Gaubitz M, Wessoleck E, Heuft G, Pfleiderer B. Altered brain activity during pain processing in fibromyalgia. Neuroimage. 2009;44(2):502-8.
20. Schrepf A, Harper DE, Harte SE, Wang H, Ichesco E, Hampson JP, et al. Endogenous opioidergic dysregulation of pain in fibromyalgia: a PET and fMRI study. Pain. 2016;157(10):2217.
21. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis & Rheumatism. 2002;46(5):1333-43.
22. Busch AJ, Barber KA, Overend TJ, Peloso PMJ, Schachter CL. Exercise for treating fibromyalgia syndrome. Cochrane database of systematic reviews. 2007 (4).
23. Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain. 2006;122(1-2):197-209.
24. DaSilva AF, Mendonca ME, Zaghi S, Lopes M, DosSantos MF, Spierings EL, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. Headache: The Journal of Head and Face Pain. 2012;52(8):1283-95.
25. Antal A, Terney D, Kühnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. Journal of pain and symptom management. 2010;39(5):890-903.
26. Fenton BW, Palmieri PA, Boggio P, Fanning J, Fregni F. A preliminary study of transcranial direct current stimulation for the treatment of refractory chronic pelvic pain. Brain stimulation. 2009;2(2):103-7.
27. Vaseghi B, Zoghi M, Jaberzadeh S. Does anodal transcranial direct current stimulation modulate sensory perception and pain? A meta-analysis study. Clinical Neurophysiology. 2014;125(9):1847-58.
28. Fregni F, Freedman S, Pascual-Leone A. Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. The Lancet Neurology. 2007;6(2):188-91.
29. O'connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. Cochrane database of systematic reviews. 2018 (3).
30. Zhu C-E, Yu B, Zhang W, Chen W-H, Qi Q, Miao Y. Effectiveness and safety of transcranial direct current stimulation in fibromyalgia: a systematic review and meta-analysis. Journal of rehabilitation medicine. 2017;49(1):2-9.
31. Fregni F, Gimenes R, Valle AC, Ferreira MJ, Rocha RR, Natalle L, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 2006;54(12):3988-98.
32. Fagerlund AJ, Hansen OA, Aslaksen PM. Transcranial direct current stimulation as a treatment for patients with fibromyalgia: a randomized controlled trial. Pain. 2015;156(1):62-71.
33. Carvalho F, Brietzke AP, Gasparin A, dos Santos FP, Vercelino R, Ballester RF, et al. Home-based transcranial direct current stimulation device development: an updated protocol used at home in healthy subjects and fibromyalgia patients. JoVE (Journal of Visualized Experiments). 2018 (137):e57614.
34. Brunoni AR, Valiengo L, Baccaro A, Zanao TA, de Oliveira JF, Goulart A, et al. The sertraline vs electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA psychiatry. 2013;70(4):383-91.
35. Hazime F, Baptista A, de Freitas D, Monteiro R, Maretto R, Hasue R, et al. Treating low back pain with combined cerebral and peripheral electrical stimulation: A randomized, double-blind, factorial clinical trial. European Journal of Pain. 2017;21(7):1132-43.
36. Viana R, Laurentino G, Souza R, Fonseca J, Silva Filho E, Dias S, et al. Effects of the addition of transcranial direct current stimulation to virtual reality therapy after stroke: a pilot randomized controlled trial. NeuroRehabilitation. 2014;34(3):437-46.

37. Mendonca ME, Simis M, Grecco LC, Battistella LR, Baptista AF, Fregni F. Transcranial direct current stimulation combined with aerobic exercise to optimize analgesic responses in fibromyalgia: a randomized placebo-controlled clinical trial. Frontiers in human neuroscience. 2016;10:68.
38. Ellingson LD, Stegner AJ, Schwabacher IJ, Koltyn KF, Cook DB. Exercise Strengthens Central Nervous System Modulation of Pain in Fibromyalgia. Brain sciences. 2016 Feb 26;6(1). PubMed PMID: 26927193. PMCID: PMC4810178. Epub 2016/03/02. eng.
39. Theadom A, Cropley M, Smith HE, Feigin VL, McPherson K. Mind and body therapy for fibromyalgia. The Cochrane database of systematic reviews. 2015 Apr 9(4):Cd001980. PubMed PMID: 25856658. Epub 2015/04/10. eng.
40. Castillo-Saavedra L, Gebodh N, Bikson M, Diaz-Cruz C, Brandao R, Coutinho L, et al. Clinically Effective Treatment of Fibromyalgia Pain With High-Definition Transcranial Direct Current Stimulation: Phase II Open-Label Dose Optimization. The journal of pain : official journal of the American Pain Society. 2016 Jan;17(1):14-26. PubMed PMID: 26456677. PMCID: PMC5777157. Epub 2015/10/13. eng.
41. Villamar MF, Wivatvongvana P, Patumanond J, Bikson M, Truong DQ, Datta A, et al. Focal modulation of the primary motor cortex in fibromyalgia using 4x1-ring high-definition transcranial direct current stimulation (HD-tDCS): immediate and delayed analgesic effects of cathodal and anodal stimulation. The journal of pain : official journal of the American Pain Society. 2013 Apr;14(4):371-83. PubMed PMID: 23415877. Epub 2013/02/19. eng.
42. Borckardt JJ, Bikson M, Frohman H, Reeves ST, Datta A, Bansal V, et al. A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. The journal of pain : official journal of the American Pain Society. 2012 Feb;13(2):112-20. PubMed PMID: 22104190. Epub 2011/11/23. eng.
43. ACSM. ACSM's Guidelines for Exercise Testing and Prescription. 9th ed: Lippincott Williams & Wilkins; 2015.
44. Stephens S, Feldman BM, Bradley N, Schneiderman J, Wright V, Singh-Grewal D, et al. Feasibility and effectiveness of an aerobic exercise program in children with fibromyalgia: results of a randomized controlled pilot trial. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2008;59(10):1399-406.
45. Oliveira N, dos Santos Sabbag L, de Sa Pinto A, Borges C, Lima F. Aerobic exercise is safe and effective in systemic sclerosis. International journal of sports medicine. 2009;30(10):728-32.
46. Gill TM, DiPietro L, Krumholz HM. Role of exercise stress testing and safety monitoring for older persons starting an exercise program. Jama. 2000;284(3):342-9.
47. Roveda F, Middlekauff HR, Rondon MUP, Reis SF, Souza M, Nastari L, et al. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. Journal of the American College of Cardiology. 2003;42(5):854-60.
48. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews. 2017 (4).
49. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of physiology. 2000;527(3):633-9.
50. Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clinical neurophysiology. 2006;117(4):845-50.
51. Potvin S, Marchand S. Pain facilitation and pain inhibition during conditioned pain modulation in fibromyalgia and in healthy controls. Pain. 2016;157(8):1704-10.
52. Granot M, Weissman-Fogel I, Crispel Y, Pud D, Granovsky Y, Sprecher E, et al. Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: do conditioning stimulus painfulness, gender and personality variables matter? Pain. 2008;136(1-2):142-9.

53. Nirl RR, Granovskyl Y, Yarnitskyl D, Sprecherl E, Granotl M. A psychophysical study of endogenous analgesia: the role of the conditioning pain in the induction and magnitude of conditioned pain modulation. European journal of pain. 2011;15(5):491-7.
54. Bosma RL, Mojarad EA, Leung L, Pukall C, Staud R, Stroman PW. F MRI of spinal and supra-spinal correlates of temporal pain summation in fibromyalgia patients. Human brain mapping. 2016;37(4):1349-60.
55. Craggs JG, Staud R, Robinson ME, Perlstein WM, Price DD. Effective connectivity among brain regions associated with slow temporal summation of C-fiber-evoked pain in fibromyalgia patients and healthy controls. The Journal of Pain. 2012;13(4):390-400.
56. Staud R, Weyl EE, Riley III JL, Fillingim RB. Slow temporal summation of pain for assessment of central pain sensitivity and clinical pain of fibromyalgia patients. PloS one. 2014;9(2):e89086.
57. Vierck Jr CJ, Cannon RL, Fry G, Maixner W, Whitsel BL. Characteristics of temporal summation of second pain sensations elicited by brief contact of glabrous skin by a preheated thermode. Journal of neurophysiology. 1997;78(2):992-1002.
58. Williams JA, Pascual-Leone A, Fregni F. Interhemispheric modulation induced by cortical stimulation and motor training. Physical therapy. 2010;90(3):398-410.
59. Rossini PM, Micera S, Benvenuto A, Carpaneto J, Cavallo G, Citi L, et al. Double nerve intraneural interface implant on a human amputee for robotic hand control. Clinical neurophysiology. 2010;121(5):777-83.
60. Li H, Huang G, Lin Q, Zhao JL, Lo WA, Mao YR, et al. Combining Movement-Related Cortical Potentials and Event-Related Desynchronization to Study Movement Preparation and Execution. Frontiers in neurology. 2018;9:822. PubMed PMID: 30344504. PMCID: PMC6182054. Epub 2018/10/23. eng.
61. Duann JR, Chiou JC. A Comparison of Independent Event-Related Desynchronization Responses in Motor-Related Brain Areas to Movement Execution, Movement Imagery, and Movement Observation. PLoS One. 2016;11(9):e0162546. PubMed PMID: 27636359. PMCID: PMC5026344. Epub 2016/09/17. eng.
62. Neuper C, Wortz M, Pfurtscheller G. ERD/ERS patterns reflecting sensorimotor activation and deactivation. Progress in brain research. 2006;159:211-22. PubMed PMID: 17071233. Epub 2006/10/31. eng.
63. Nuwer MR, Lehmann D, Silva FLd, Matsuoka S, Sutherling W, Vibert J-F. IFCN guidelines for topographic and frequency analysis of EEGs and EPs. Report of an IFCN committee. Electroencephalography and clinical Neurophysiology. 1994;91(1):1-5.
64. Liu C, Wang H, Pu H, Zhang Y, Zou L, editors. EEG feature extraction and pattern recognition during right and left hands motor imagery in brain-computer interface. 2012 5th International Conference on BioMedical Engineering and Informatics; 2012: IEEE.
65. Ribeiro H, Sesterhenn RB, Souza A, Souza AC, Alves M, Machado JC, et al. Preoperative transcranial direct current stimulation: Exploration of a novel strategy to enhance neuroplasticity before surgery to control postoperative pain. A randomized sham-controlled study. PLoS One. 2017;12(11):e0187013. PubMed PMID: 29190741. PMCID: PMC5708693. Epub 2017/12/01. eng.
66. Braulio G, Passos SC, Leite F, Schwertner A, Stefani LC, Palmer ACS, et al. Effects of Transcranial Direct Current Stimulation Block Remifentanil-Induced Hyperalgesia: A Randomized, Double-Blind Clinical Trial. Frontiers in pharmacology. 2018;9:94. PubMed PMID: 29515438. PMCID: PMC5825908. Epub 2018/03/09. eng.
67. Flood A, Waddington G, Keegan RJ, Thompson KG, Cathcart S. The effects of elevated pain inhibition on endurance exercise performance. PeerJ. 2017;5:e3028. PubMed PMID: 28265507. PMCID: PMC5337081. Epub 2017/03/08. eng.

68. Flood A, Waddington G, Cathcart S. High-Definition Transcranial Direct Current Stimulation Enhances Conditioned Pain Modulation in Healthy Volunteers: A Randomized Trial. The journal of pain : official journal of the American Pain Society. 2016 May;17(5):600-5. PubMed PMID: 26844419. Epub 2016/02/05. eng.

69. da Silva NR, Laste G, Deitos A, Stefani LC, Cambraia-Canto G, Torres IL, et al. Combined neuromodulatory interventions in acute experimental pain: assessment of melatonin and non-invasive brain stimulation. Frontiers in behavioral neuroscience. 2015;9:77. PubMed PMID: 25873871. PMCID: PMC4379934. Epub 2015/04/16. eng.

70. Meeus M, Hermans L, Ickmans K, Struyf F, Van Cauwenbergh D, Bronckaerts L, et al. Endogenous pain modulation in response to exercise in patients with rheumatoid arthritis, patients with chronic fatigue syndrome and comorbid fibromyalgia, and healthy controls: a double-blind randomized controlled trial. Pain practice : the official journal of World Institute of Pain. 2015 Feb;15(2):98-106. PubMed PMID: 24528544. Epub 2014/02/18. eng.

71. Garcia-Hermoso A, Saavedra JM, Escalante Y. Effects of exercise on functional aerobic capacity in adults with fibromyalgia syndrome: A systematic review of randomized controlled trials. Journal of back and musculoskeletal rehabilitation. 2015;28(4):609-19. PubMed PMID: 25408119. Epub 2014/11/20. eng.

72. Bidonde J, Busch AJ, Schachter CL, Overend TJ, Kim SY, Goes SM, et al. Aerobic exercise training for adults with fibromyalgia. The Cochrane database of systematic reviews. 2017 Jun 21;6:Cd012700. PubMed PMID: 28636204. PMCID: PMC6481524. Epub 2017/06/22. eng.

73. Wang C, Schmid CH, Fielding RA, Harvey WF, Reid KF, Price LL, et al. Effect of tai chi versus aerobic exercise for fibromyalgia: comparative effectiveness randomized controlled trial. BMJ (Clinical research ed). 2018 Mar 21;360:k851. PubMed PMID: 29563100. PMCID: PMC5861462 at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from National Center for Complementary and Integrative Health at the National Institutes of Health in the US for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. Epub 2018/03/23. eng.

74. Marske C, Bernard N, Palacios A, Wheeler C, Preiss B, Brown M, et al. Fibromyalgia with Gabapentin and Osteopathic Manipulative Medicine: A Pilot Study. Journal of alternative and complementary medicine (New York, NY). 2018 Apr;24(4):395-402. PubMed PMID: 29298077. Epub 2018/01/04. eng.

75. Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity on perceived symptoms and physical function in adults with fibromyalgia: results of a randomized trial. Arthritis Res Ther. 2010;12(2):R55. PubMed PMID: 20353551. PMCID: PMC2888205. Epub 2010/04/01. eng.

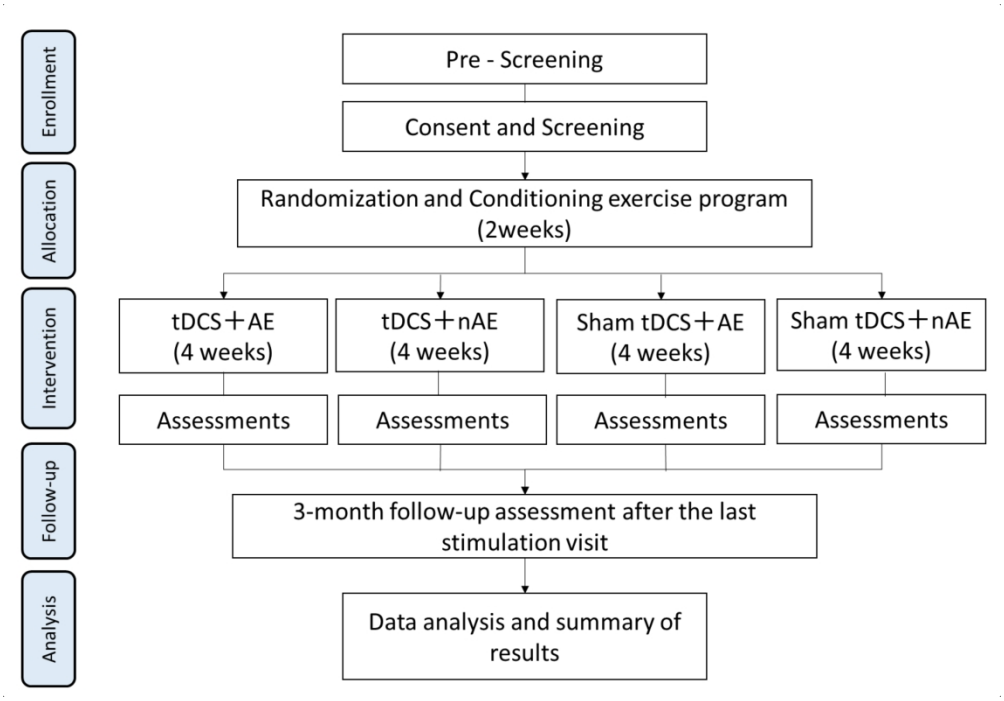
76. Valle A, Roizenblatt S, Botte S, Zaghi S, Riberto M, Tufik S, et al. Efficacy of anodal transcranial direct current stimulation (tDCS) for the treatment of fibromyalgia: results of a randomized, sham-controlled longitudinal clinical trial. Journal of pain management. 2009;2(3):353-61. PubMed PMID: 21170277. PMCID: PMC3002117. Epub 2009/01/01. eng.

77. Möller H-J, Müller H, Borison RL, Schooler NR, Chouinard G. A path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in schizophrenic patients. European archives of psychiatry and clinical neuroscience. 1995;245(1):45-9.

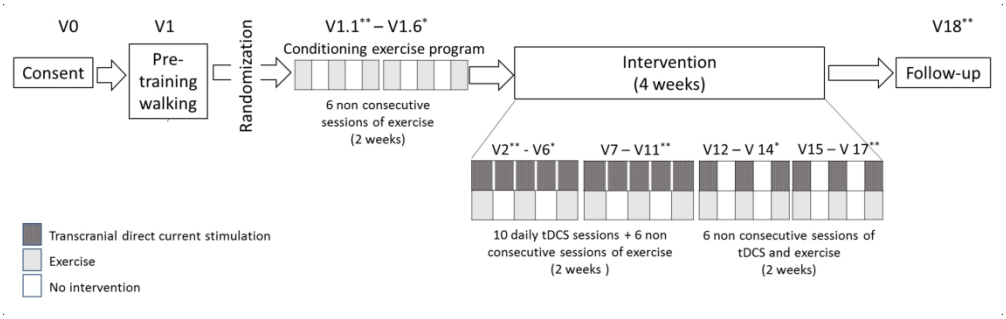
Figure Legends:

Figure 1 Flow chart of the study based on CONSORT criteria.

Figure 2 Schematic view of the timeline



Flow chart of the study based on CONSORT criteria.



Schematic view of the timeline

Trial registration dataset	
Data Category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03371225
Date of registration in primary registry	December 13, 2017
Secondary identifying numbers	2017P002524
Source of monetary or material support	National Institutes of Health (NIH)
Primary sponsor	National Institutes of Health (NIH)
Contact for public queries	Felipe Fregni, MD, PhD, MPh, MMSc
Contact for scientific queries	Felipe Fregni, MD, PhD, MPh, MMSc
Public title	Optimized tDCS for fibromyalgia: targeting the endogenous pain control system
Scientific title	Optimized tDCS for fibromyalgia – targeting the endogenous pain control system: A randomized, double-blind, factorial clinical trial protocol
Countries of recruitment	United States
Health condition(s) or problem(s) studies	Fibromyalgia
Interventions	Device: Active tDCS; Procedure: Active Exercise; Device: Sham tDCS; Procedure: Sham Exercise
Key inclusion and exclusion criteria	**Inclusion criteria:** 1) 18-65 years; 2) Diagnosis of FM pain according to the ACR 2010 criteria; 3) Pain resistant to common analgesics and medications for chronic pain; 4) Must have the ability to feel sensation by Von-Frey fiber on the forearm; 5) Able to provide informed consent to participate in the study. **Exclusion criteria:** 1) Clinically significant or unstable medical or psychiatric disorder; 2) History of substance abuse within the past 6 months as self-reported; 3) Previous significant neurological history; 4) Previous neurosurgical procedure with craniotomy; 5) Severe depression; 6) Pregnancy; 7) Current opiate use in large doses; 8) increased risk for exercise

Study type	Interventional
	Randomized, double-blind, factorial clinical trial
Date of first enrolment	May 2019
Target sample size	148
Recruitment status	Recruiting
Primary outcome(s)	Conditioned Pain Modulation (CPM); Temporal Slow Pain Summation (TSPS)
Key secondary outcomes	Intracortical inhibition assessed by TMS; thalamocortical dysrhythmia (TCD) and event related desynchronization (ERD) assessed by EEG; Average pain intensity as assessed by Modified Brief Pain Inventory (BPI); Revised Fibromyalgia Impact Questionnaire (FIQ-R); Quality of life assessed by Quality of Life Scale (QoLS), Patient Reported Outcomes Measurement Information System (PROMIS); Pittsburgh Sleep Quality Index (PSQI) and Beck Depression Inventory (BDI).

Protocol Version:
Issue date: 05/16/2019
Protocol amendment number: 08

Revision Chronology
18/01/2018: Original submission
08/23/2018: Amendment 01- Primary reason for amendment: clarification of inclusion/exclusion criteria
11/02/2018: Amendment 04 - Primary reason for amendment: clarification of TMS protocol
16/05/2019: Amendment 08- Primary reason for amendment: clarification of CPM and TSPS procedures

All other Amendments (01, 03, 05, 06, 07) were related to changes in study staff. Any further amendments will follow Partners Healthcare institutional policies.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	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	11
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a. Supplementary file
Protocol version	#3	Date and version identifier	n/a. Supplementary file
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	11

contributorship				
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a. NIH funded	
Roles and responsibilities: sponsor and funder	#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	n/a. NIH funded	
Roles and responsibilities: committees	#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)	n/a- PI oversees the study	
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
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators		3
Objectives	#7	Specific objectives or hypotheses		3
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, non-inferiority, exploratory)		4
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	4
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)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#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)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	7
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)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions	9

		supporting any sample size calculations		
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size		4
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		4
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		4
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions		4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how		4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a. We do not anticipate circumstances that would require emergency unblinding	
Methods: Data collection, management, and analysis				
Data collection plan	#18a	Plans for assessment and collection of outcome,		10

		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	
Data collection plan: retention	#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	10
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	10
Statistics: outcomes	#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	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#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)	11
Methods: Monitoring			
Data monitoring: formal committee	#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,	11

		an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#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	n/a. No interim analyses will be performed
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	6
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
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)	n/a. Supplementary file
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	2

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
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	n/a
Dissemination policy: trial results	#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	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	There will be no use of professional writers. Authorship will be decided among study personnel with intellectual contributions.
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Informed consent follows Partners Healthcare institutional policies
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	n/a. There will be no collection of biological specimens/a. There will be no collection of biological specimens.

Notes:

- 2b: n/a. Supplementary file
- 3: n/a. Supplementary file

- 5b: n/a. NIH funded
- 5c: n/a. NIH funded
- 5d: n/a- PI oversees the study
- 17b: n/a. We do not anticipate circumstances that would require emergency unblinding
- 21b: n/a. No interim analyses will be performed
- 25: n/a. Supplementary file
- 31b: There will be no use of professional writers. Authorship will be decided among study personnel with intellectual contributions.
- 32: Informed consent follows Partners Healthcare institutional policies
- 33: n/a. There will be no collection of biological specimens/a. There will be no collection of biological specimens. The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 01. July 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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Optimized transcranial direct current stimulation (tDCS) for fibromyalgia – targeting the endogenous pain control system: A randomized, double-blind, factorial clinical trial protocol

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Rehabilitation medicine, Research methods, Rheumatology
Keywords:	transcranial direct current stimulation, aerobic exercise, fibromyalgia, endogenous pain control system, temporal slow pain summation,

	conditioned pain modulation

Optimized transcranial direct current stimulation (tDCS) for fibromyalgia – targeting the endogenous pain control system: A randomized, double-blind, factorial clinical trial protocol

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ABSTRACT

Introduction

Fibromyalgia is a common debilitating condition with limited therapeutic options. Medications have low efficacy and are often associated with adverse effects. Given that FM is associated with a defective endogenous pain control system and central sensitization, combining interventions such as transcranial direct current stimulation (tDCS) and aerobic exercise to modulate pain-processing circuits may enhance pain control.

Methods and analysis

A prospective, randomized (1:1:1:1), placebo-controlled, double-blind, factorial clinical trial will test the hypothesis that optimized tDCS (16 anodal tDCS sessions combined with aerobic exercise) can restore of the pain endogenous control system. Participants with FM (n=148) will undergo a conditioning exercise period and be randomly allocated to one of four groups: (1) active tDCS and aerobic exercise (2) sham tDCS and aerobic exercise, (3) active tDCS and non-aerobic exercise, or (4) sham tDCS and non-aerobic exercise. Pain inhibitory activity will be assessed using conditioned pain modulation (CPM) and temporal slow pain summation (TSPS) – primary outcomes. Secondary outcomes will include the following assessments: Transcranial Magnetic Stimulation (TMS) and electroencephalography (EEG) as cortical markers of pain inhibitory control and thalamocortical circuits; secondary clinical outcomes on pain, fibromyalgia impact, quality of life, sleep and depression. Finally, the relationship between the two main mechanistic targets in this study – CPM and TSPS – and changes in secondary clinical outcomes will be tested. The change in the primary efficacy endpoint, CPM and TSPS, from baseline to week 4 of stimulation will be tested with a mixed linear model and adjusted for important demographic variables.

Ethics and dissemination

This study obeys the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Partners Healthcare under the protocol number 2017P002524. Informed consent will be obtained from participants. Study findings will be reported in conferences and peer-reviewed journal publications.

Trial registration
NCT03371225

Strengths and Limitations

- A sham-controlled, powered clinical trial on a novel low-cost therapy for fibromyalgia.
- Endogenous pain system biomarkers will help reveal the mechanisms of fibromyalgia as well as the interventions.
- This study will inform us on the number of sessions needed to induce significant changes in neuroplasticity reflected in the above mentioned markers.
- The secondary outcomes of this study will evaluate the suitability of the proposed biomarkers to predict treatment response.
- Exclusion of patients with increased risk during exercise may limit the generalizability of the findings.

INTRODUCTION

Fibromyalgia (FM) affects about 2% of the world population (1) and is associated with poor quality of life mainly due to pain, fatigue, sleep disturbances, functional limitations and cognitive impairments (2). Current treatments for this challenging complex condition for FM lead to an average annual cost of $5,945 in insurance claims per FM patient, more than twice the amount of a typical beneficiary (3). The treatment of choice is a multimodal approach that includes self-management strategies (4), but there is a large gap between supply and demand as access to such therapies is limited. Consequently, many FM patients rely on pharmaceuticals such as nonsteroidal anti-inflammatory drugs, antidepressants, and/or anticonvulsants, which usually do not provide enough symptom relief and are frequently associated with adverse effects (5). Therefore, there is an urgent need for the development of novel and targeted treatments with fewer side-effects.

Rationale and gap

Accumulating evidence (6-9) shows that disturbances in the endogenous pain control system lead to chronic pain. Several neurophysiological (10-16) and neuroimaging (17-21) studies showed altered pain processing mechanisms in FM; therefore, therapies that target and modulate the neural circuits involved in pain control are essential to treat FM characteristic chronic widespread pain. Different ways to potentially modulate these circuits include exercise- which has a known evidence-based therapeutic effect on pain in FM (22), and non-invasive neuromodulation techniques such as transcranial direct current stimulation (tDCS)- which demonstrably improve several chronic pain conditions (23-28). Despite its investigated benefits to treat different pain conditions (typically targeting the primary motor cortex (M1)), tDCS effects in FM have been mixed (29-32). Yet tDCS can be easily coupled to other therapies due to its low-cost and portability (33), and such combinations have been superior to either of the therapies alone in other disorders (34-36). We have shown in a pilot study with 45 FM subjects that combining exercise and tDCS for FM leads to a significant pain decrease that also shows a different neural signature as compared to each therapy alone (tDCS or exercises) (37). In this initial study, however, the endogenous pain inhibitory system was not assessed.

Given the extensive data showing that (i) FM has a defective endogenous pain inhibitory system (10-16) and (ii) exercises (38-40) and TDCS lead to modulation of this system (31, 41, 42), we then hypothesized that these two neuromodulatory techniques can help restore the endogenous pain inhibitory system in FM. Neurophysiological and clinical assessments including Electroencephalography (EEG), Transcranial Magnetic Stimulation (TMS), quantitative sensory testing and questionnaires for pain and quality of life can provide important data to understand how the endogenous pain inhibitory system is then modulated by these two interventions.

Research question and hypothesis

We therefore aimed to test whether in subjects with FM 16 sessions of M1 anodal tDCS combined with aerobic exercise decrease temporal slow pain summation (TSPS) and increase conditioned pain modulation (CPM) responses compared to each intervention alone and to sham when assessed on the last day of intervention. We hypothesize that this optimized tDCS plus aerobic exercise technique will lead to a stronger engagement of the endogenous pain regulatory system, which will ultimately lead to increased pain regulation in patients with FM.

Objectives

Primary objective:

- To evaluate the effects of 4 weeks of tDCS plus aerobic exercise on the endogenous pain regulatory system (assessed by CPM) and central sensitization (assessed by TSPS) compared to either interventions alone and to no intervention.

Secondary objectives:

- To determine the effect of these interventions on cortical markers of inhibitory control that are also altered in FM, such as intracortical inhibition assessed by TMS, and changes in thalamocortical dysrhythmia (TCD) and event related desynchronization (ERD) assessed by EEG;
- To assess whether engagement of the two main targets tested in this study (TSPS and CPM) are associated with the secondary clinical outcomes (i.e. changes in pain outcomes: Brief Pain Inventory, Revised Fibromyalgia Impact Questionnaire);
- To assess EEG changes across groups and their suitability as potential markers of TCD normalization;
- To determine the number of sessions needed to induce significant changes in markers of the endogenous pain inhibitory system and central sensitization (CPM and TSPS) and cortical changes (paired pulse TMS and EEG).

METHODS AND ANALYSIS

Trial Design

This is a single center 4-arm factorial RCT. Participants will be randomized using a random blocked randomization sequence generated by a computer software. We used a 1:1:1:1 allocation ratio to active or sham tDCS combined with aerobic (AE) or non-aerobic exercise (nAE) on the first day of the conditioning exercise program. The staff member performing randomization will not be involved in the trial otherwise. Sequentially numbered sealed envelopes will maintain allocation concealment. Investigators providing assessments will be blinded to tDCS but not exercise. Assessors of primary and secondary outcomes (and participants) will be blinded to group allocation. (See Figure 1 for group allocation).

Study setting

This is a single-site study, all procedures will be conducted at the Neuromodulation Center, Spaulding Rehabilitation Hospital. Enrollment start date is May 1, 2019 and expected end date is December 31, 2023.

Eligibility Criteria

We will use broad-based recruitment strategies, including online advertisements, flyers, clinician referrals, etc. All eligible participants must fulfill the inclusion criteria and have none of the exclusion criteria listed in **Table 1.**

Table 1: Inclusion and exclusion criteria

Inclusion criteria:

1) Age range 18-65 years,

2) Diagnosis of FM pain according to the ACR 2010 criteria (existing pain for more than 6 months with an average of at least 4 on a 0-10 VAS scale) without other comorbid chronic pain diagnosis,

3) Pain resistant to common analgesics and medications for chronic pain such as Tylenol, Aspirin, Ibuprofen, Soma, Parafon Forte DCS, Zanaflex, and Codeine,

4) Must have the ability to feel sensation by Von-Frey fiber on the forearm,

5) Able to provide informed consent to participate in the study.

Exclusion criteria:

1) Clinically significant or unstable medical or psychiatric disorder,

2) History of substance abuse within the past 6 months as self-reported (if subject reports a history of substance abuse, we will confirm using DSM V criteria),

3) Previous significant neurological history (e.g., traumatic brain injury), resulting in neurological deficits, such as cognitive or motor deficits, as self-reported,

4) Previous neurosurgical procedure with craniotomy,

5) Severe depression (with a score of >30 on the Beck Depression Inventory),

6) Pregnancy - as the safety of tDCS in pregnant population (and children) has not been assessed (though the risk is non-significant), we will exclude pregnant women (and children). Women of child-bearing age will be required to take a urine pregnancy test during the screening process and in every week of stimulation),

7) Current opiate use in large doses (more than 30mg of oxycodone/hydrocodone or 7.5mg of hydromorphone (Dilaudid) or equivalent),

8) Patients will be excluded when they have increased risk for exercise defined as (i) not fulfilling the American College Of Sports Medicine (ACSM) criteria (i.e. risk of cardiovascular complication (43)) and in this case not cleared by a licensed physician.

As part of the eligibility criteria, participants will perform a pre-training visit to evaluate if they are comfortable with walking on the treadmill at a self-selected speed at their baseline heart rate (HR) for 30 minutes. Only subjects comfortable with this task will be randomized. If the subject is unable to walk for 30 minutes on the treadmill or reports discomfort or any side-effects precluding physical exercise (e.g., excessive muscle soreness), they will be screened out. Also, a demographic survey will be taken during the consent visit.

Intervention

Exercise

Conditioning exercise program: 6 exercise sessions are divided in 3 days per week over 2 weeks. Duration of sessions will start with 10 minutes and increase gradually, ending with a 30-minute session on the last day. The AE group will walk briskly at 60-70% of their maximum Heart Rate (HR) and the nAE group will walk within 5% of their baseline HR. If a participant on the AE group is unable to progress beyond 15 min at 60-70% HR max over the initial 2 weeks, they will be screened out of the study. After the conditioning exercise program, subjects will continue with the intervention part of the protocol. Participants will complete aerobic or non-aerobic exercise 3 times a week on nonconsecutive days over 4 weeks.

Aerobic exercise (AE): Participants will undergo moderate intensity AE on a treadmill over 30 minutes (American Heart Association recommendation for adults). HR will be monitored throughout the entire procedure by a sensor. The investigator will sequentially increase the treadmill speed by 0.1 mph every 5 seconds, until the participant reaches 60-70% of age-predicted maximal heart rate (HRmax), following the formula HRmax = 208 − (0.7 * age), as this has been found safe in various conditions (22, 44-48). AE intensity will be modulated based on the participant's HRmax throughout the session. If the HRmax exceeds 70%, the investigator will decrease treadmill speed by 0.1 mph every 5 seconds until returning to the 60-70% HRmax target. If HRmax reaches 80% or the subject shows any signs of discomfort, the session will be stopped.

Non-aerobic exercise (nAE): Participants will walk on the treadmill for 30 minutes with a workload intensity within 5% baseline HR, as we used this method in our preliminary study(37).

As recommended by ACSM guidelines for AE in FM patients , the participant will be questioned regarding any respiratory or cardiovascular symptoms on each visit before starting the exercise; we will monitor pain and fatigue levels after the first 5, 15 and 25 minutes of exercise using a numeric pain scale (43). Additionally, to evaluate adverse effects during AE or nAE training, we will record any musculoskeletal symptoms such as pain, muscle strain, muscle soreness, fatigue, dizziness and shortness of breath.

Transcranial Direct Current Stimulation (tDCS)

A 1x1 Low-intensity DC Stimulator, the Soterix Medical 1x1 tDCS-Clinical Trial, will be used with codes corresponding to active or sham stimulation, allowing a double-blinded procedure. Participants will receive 16 tDCS sessions over 4 weeks of treatment. Weeks 1 and 2 will begin with 5 consecutive days of tDCS followed by Weeks 3 and 4 with 3 alternating days of tDCS. The exercise and the tDCS will be performed simultaneously as explained on Figure 2.

Active (anodal) tDCS: During active tDCS, a 2mA constant current will be delivered for 20 minutes through rubber electrodes encased in 35 cm^2 saline-soaked sponges. The anode will be placed over the left primary motor cortex (M1) and the cathode over the contralateral supraorbital area. M1 will be localized using the 10/20 International EEG System (C3 – adapted by measuring 5 cm below the vertex), a reliable method for tDCS(23).

Sham tDCS: We will use the same montage and parameters as active tDCS, but the active current will be applied for 30 seconds in the beginning and at the end of the procedure to simulate the same sensations of

the current ramping as in active stimulation (49). Using 30 seconds of ramping is reliable for blinding (50) and less than 3 minutes of tDCS induces no cortical excitability effects (49).

A TDCS adverse events questionnaire will be administered after each stimulation session. Subjects will be instructed not to use other methods of electrical stimulation during the trial.

Outcomes

Evaluation of Endogenous Pain Inhibition System (Primary Outcomes)
During the CPM and TSPS protocols, heat pulses will be generated by a TSA-II Stimulator (Medoc Advanced Medical Systems, Ramat Yishai, Israel) delivered to the right proximal volar forearm using a 30mm x 30mm embedded heat pain (HP) thermode. A minimum interval of 10 minutes between the two assessments will be respected.

Conditioned pain modulation (CPM) evaluates the ability to inhibit pain. When a pain test stimulus is given together with a conditioning pain stimulus, the test stimulus is perceived as less painful than when it was given alone (51). We will follow the adapted protocol suggested by Granot et al., 2008(52) and Nirl et al., 2011(53). We will first determine the pain-60 test temperature (which is the temperature that induces pain sensation at a magnitude of 60 on a 60-100 numerical pain scale (NPS)) by applying a Peltier thermode (Medoc Advanced Medical Systems, Ramat Yishai, Israel) on the right forearm and delivering three short heat stimuli (43, 44, and 45 °C), each lasting 7 seconds (starting from the time the stimulus intensity reaches the destination temperature). Subjects will be asked to rate the level of pain intensity using a numerical pain scale (NPS) ranging from 0 = "no pain'' to 100 = "the worst pain imaginable''. If the first temperature of 43 °C is considered too painful (>60/100), we will stop the series and will provide additional stimuli at lower temperatures of 41 and 42 °C. If the three temperatures (43, 44, and 45 °C) are unable to achieve pain-60, we will deliver additional stimuli at 46, 47, and 48 °C until reaching the desired pain level of 60/100; in the unlikely event that none of those temperatures elicits pain-60, we will consider it to be 48°C. On determining the pain-60 temperature, we will administer the test stimulus at that temperature for 30s, and subjects will be asked to rate their pain intensity at 10, 20 and 30s after the thermode reaches the pain-60 temperature (mean scores of the three pain ratings will be calculated). Five minutes after delivering the test stimulus, the conditioning stimulus will be applied: the subject's left hand will be immersed for 30s in a water bath set at 10-12°C. Then the same pain-60 temperature will be applied to the right forearm (left hand will still be immersed) for 30s and the subject will again be asked to rate their pain intensity 3 times after the thermode reaches the pain-60 temperature: at 10, 20 and 30s (mean scores of the three pain ratings will be calculated). CPM response will be calculated as the difference between the average of pain ratings from the test stimulus minus the average of pain ratings during the conditioned stimulus.

Temporal slow pain summation (TSPS) represents summation of C fiber mediated pain, assesses central sensitivity, and is used to probe pain processing abnormalities in several chronic pain disorders (54, 55). Subjects will be trained to identify pain-60 test temperature (see CPM protocol above) and we will follow the adapted protocol suggested by Staud et al., 2014 (56) in which the HP-thermode was programmed to deliver pulses with rise/fall of 1-2s, depending on subject's pain-60 level, from adapting temperatures to peak temperatures, with a plateau of 0.7s. They will receive 1 train of 15 repetitive heat stimuli at 0.4 Hz, which (being suitable to elicit TSPS in most subjects) allows the rating of individual pain stimuli and is

unlikely to induce peripheral sensitization (57). TSPS will be calculated as the difference between heat pain rating after the 1st and 15th stimuli.

Evaluation of cortical markers of inhibitory control (Secondary Neurophysiological Outcomes)

Transcranial magnetic stimulation (TMS)

To assess tDCS and AE effects we will measure the excitability of pain-related pathways using TMS markers. TMS assessments will be similar to our previous study (58). Single pulse TMS will be performed to acquire resting motor threshold (rMT) and motor evoked potentials (MEPs); paired pulse technique will measure short interval cortical inhibition (SICI) and intracortical facilitation (ICF). We will use Magstim Rapid^2 device with a figure-of-eight magnetic stimulator coil placed on the right and left M1 (for all assessments) and will record surface electromyogram (EMG) from the contralateral first dorsal interosseous (FDI) muscle. TMS data will be recorded and stored in a computer for off-line analysis.

1. *Resting motor threshold (rMT)*: Initially we will investigate rMT following the technique described by Rossini and colleagues, where rMT is defined as the lowest stimulus intensity to evoke a MEP of 100 μV in 3/5 trials in the relaxed muscle (59).

2. *Motor evoked potential*: We will initially adjust TMS machine output intensity to achieve a baseline MEP of 1 mV peak-to-peak amplitude before the intervention. Stimulation intensity will be kept constant for each subject throughout the evaluation sessions. We will record 10 MEPs for each assessment and average their peak-to-peak amplitudes and areas-under the-curve.

3. *Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF):* We will use paired pulse testing with a subthreshold conditioning stimulus (80% rMT) followed by a suprathreshold test stimulus of 120 % of the motor threshold. Interstimulus intervals will be 2ms for SICI and 10ms for ICF. Ten randomized stimuli will be applied at each interval and the percentage of inhibition or facilitation for each interstimulus interval before and after treatment will be calculated. The paired pulse MEP intensity will be the machine output intensity eliciting 1 mV peak-to-peak amplitude that day – not the baseline MEP intensity used for single pulse testing. If we cannot obtain rMT, we will not perform MEPs or paired pulse.

Electroencephalography (EEG)

EEG will take place over approximately 45 min: 25 minutes of participant and software preparation, 10 minutes of EEG recording divided into a resting EEG condition (5 minutes with eyes open, 5 minutes with eyes closed), and a task-related condition (8 minutes). Participants will be asked to relax in the resting condition; the investigator will ensure they do not fall asleep.

The task-related condition will include movement observation (MO), movement imagery (MI) and movement execution (ME). This will be recorded by connecting the Net Station software (for EGI) with E-Prime®. The entire task-related condition part will consist of 60 trials, with 20 trials for each of MO, MI and ME in a randomized order (60, 61). Each trial will involve initial fixation (on a cross on a screen), followed by a visual cue stating the task to be performed ("imagine" and "clench"), and a video will automatically play for observation. During each MO trial, the participant will view a video of a right hand

clenching; during the MI task the participant will be asked to imagine clenching her/his right hand once, and during the ME task the subject will be asked to clench her/his right hand once. There will be a 4 second rest period between each trial. The purpose of the task-related condition is to evaluate ERD that reflects the motor cortex activation (62).

We will record the EEG in a standardized way (63) using the 64-channel EGI system (EGI, Eugene, United States of America). The EEG will be recorded with a band-pass filter of 0.3– 200 Hz and digitized at the sampling rate of 250 Hz (64) by connecting the Net Station software (for EGI) with E-Prime®. On acquiring the EEG data, the EEGs will be inspected and artifacts will be cleaned manually. We will use EEGLAB and analysis of EEG data will include a power analysis of the power bands in the resting EEG portion - delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz) bands - fast fourier transformation (FFT), ICA decomposition, ERD responses of the three different motor tasks, functional connectivity measures and topographical analysis. The analysis will compare groups at baseline, during the stimulation period, on the last day of the intervention and at the 3-months follow-up.

Secondary Clinical Outcomes

The following secondary outcomes will be assessed: average pain intensity as assessed by Modified Brief Pain Inventory (BPI); Revised Fibromyalgia Impact Questionnaire (FIQ-R); quality of life assessed by Quality of Life Scale (QoLS), Patient Reported Outcomes Measurement Information System (PROMIS); Pittsburgh Sleep Quality Index (PSQI) and Beck Depression Inventory (BDI).

Timeline

This trial has 25 visits divided into 4 components (consent and pre-training walking, conditioning exercise program, intervention and follow-up). To increase adherence to protocol, we will adjust the calendar of sessions according to the subject's availability. See figure 2 below.

Study Sample

Our target population is individuals with FM according to the ACR 2010 criteria. We plan to enroll 148 subjects divided into 4 groups (n=37/group).

Sample Size Calculation

We used the information from trials measuring the effects of tDCS and aerobic exercise on CPM and TSPS according to different scenarios to do this sample size calculation (See Table 2 below):

- In Scenario I we considered the effects of tDCS on CPM in patients with chronic pain: this resulted in an effect size (ES) of 0.79.
- In Scenario II we evaluated the effect of tDCS on CPM in healthy volunteers: this resulted in a pooled ES of 1.02.
- In Scenario III we evaluated the effect of exercise on CPM in chronic pain and this resulted in an ES of 0.78.

Study	Population	Intervention	Effect Size
Scenario I: TDCS effect on CPM in chronic pain			
Ribeiro et al. 2017 (65)	40 women with chronic pain undergoing hallux valgus surgery	Active vs. sham tDCS.	Cohen's d = 0.79

Scenario II: TDCS effect on CPM in healthy volunteers			
Braulio et al. 2018 (66)	48 healthy males	Active-tDCS + remifentatnil vs. sham-tDCS + remifentanil	Cohen's d = 0.98
Flood et al. 2017 (67)	12 healthy males	Active HD-tDCS vs sham HD-tDCS	Cohen's d = 1.38
Flood et al. 2016 (68)	30 healthy males	Active vs. sham tDCS	Cohen's d = 0.89
Silva et al. 2015 (69)	20 healthy males	Active tDCS + melatonin vs. placebo + sham-tDCS	Cohen's d = 0.67
Pooled effect size			1.02
Scenario III: Exercise effect on CPM in chronic pain			
Meeus et al. 2015 (70)	16 rheumatoid arthritis	Exercise pre and post	Cohen's d = 0.78

Table 2: Effect size in 3 scenarios.

Based on this analysis, we decided upon a conservative approach and chose the lowest ES; thus, we used an ES of 0.78. In addition, it is important to underscore that we expect that the combination of tDCS + aerobic exercise will have a higher effect than each intervention alone (tDCS, exercise, or placebo). Additionally, in this current proposal the dosage of tDCS is higher than the studies we used to calculate the sample size (see Tables 2 and 3).

We assumed a type I error of 5% (alpha), and made a sensitivity analysis with a type 2 error (beta) of 10%, 15% and 20% (therefore a power of 90%, 85%, and 80%). We used a t-test for 2 independent means and considered dropout rates of 20% and 15%. See Table 3 below:

	Alpha	**ES**	**Dropout rate**	**Final total sample size (4 groups)**
Power of 80%	5%	0.78	15%	124
Power of 85%	5%	0.78	15%	142
Power of 90%	5%	0.78	15%	165
Power of 80%	5%	0.78	20%	130
Power of 85%	5%	0.78	20%	148
Power of 90%	5%	0.78	20%	172

Table 3: Two-tailed analyses

Although most studies used a power of 80% and a dropout rate of 10 to 15% (22, 29, 71-76) we chose a dropout rate of 20% and power of 85% as to be more conservative and also account for unexpected factors.

Data analysis

All data collected will be kept in a secured and password protected database, accessible only to IRB trained and approved study staff. All analyses will be performed as intention-to-treat in which all randomized subjects who receive at least one intervention session will be included. We will conduct sensitivity analyses and test different models of handling missing data: Last Observation Carried Forward and Multiple Imputation. The change in the primary efficacy endpoints, CPM and TSPS, from baseline to week 4, will be tested with a mixed linear regression model. This model will be adjusted for important demographic variables (e.g., gender) and baseline clinical parameters where appropriate. All tests will be two-sided (alpha level 0.05).

We will initially test our main hypothesis that active tDCS+AE increases CPM and decreases TSPS more than sham tDCS+nAE. If the effect is significant, we will then test differences between the active tDCS+AE group versus the two interventions alone. We will run a secondary mixed linear model to estimate the rate of change over time (using the secondary endpoints added in this model - Week 2 and follow-up), and also include the interaction term (treatment*time) to detect whether treatment effect changes differently over time. If the interaction is not significant, we will then test whether there is a main effect of time that is independent of treatment level (interaction will be removed from the model). We will adjust this model for important covariates such as age, gender, pain levels (NPS), and other baseline clinical outcomes where appropriate. For secondary clinical variables with significant effects, we will test whether they moderate the interventions' effects on our mechanistic (TMS and EEG) outcomes, thereby gaining additional mechanistic insights. To complete our analysis, we will apply a path analysis (77) to CPM and TSPS to determine if endogenous pain modulation changes (indexed by CPM and TSPS) associated with active tDCS+AE is related to direct effects versus indirect effects through secondary outcome improvements. We propose that a direct effect of active tDCS and AE on the endogenous pain inhibitory system can be inferred if the treatment effect cannot be explained by changes in psychological or functional outcomes.
An independent monitoring committee (IMC) will review data on recruitment, adherence and safety; meetings will occur annually, after enrollment of 25% of the target sample or in case of reports of any serious adverse events. NIH will also perform annual site monitoring visits.

Patient and public involvement
Patients and public were not involved in the design of this study.

Ethics and dissemination
This protocol was approved by the IRB at the Partners Human Research Committee (Protocol approval number: 2017P002524). All requirements regarding the welfare, rights, and privacy of human subjects protection were fulfilled. The risks of this clinical trials were considered to be minimal and are addressed in the protocol and consent form. Informed consent will be obtained from all participants before any study procedures by the Principal Investigator or co-investigators. Trial registration number: NCT03371225. For a complete list of trial registration dataset and protocol version history please refer to Supplementary File 1.

The study findings will be reported in conferences and in peer-reviewed journal publications.

Contributors: LCB and EUK are joint first authors and with FF conceptualized the paper. PGM, LCS and AEG wrote the Abstract. LCB, EUK, LCS, MEG wrote the Introduction. AC, CBP, IMT, EUK, LCB, ME, KPB, PGM, DD, AEG and YY wrote Methods and Analysis. AC, IMT and YY prepared the figures. FF, ME, WC and HR provided critical review.

Funding
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Competing Interest
The authors declare no competing interests with this research.

Ethics Approval
This study obeys the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Partners Healthcare under the protocol number 2017P002524

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement: Upon completion of the trial and after publication of the primary manuscript, we plan to provide access to the de-identified dataset following the guidelines of our institution (Spaulding Rehabilitation Hospital/Partners Healthcare and Harvard Medical School).

REFERENCES

1. Wolfe F, Brähler E, Hinz A, Häuser W. Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population. Arthritis care & research. 2013;65(5):777-85.
2. Verbunt JA, Pernot DH, Smeets RJ. Disability and quality of life in patients with fibromyalgia. Health and Quality of Life Outcomes. 2008;6(1):8.
3. Robinson RL, Birnbaum HG, Morley MA, Sisitsky T, Greenberg PE, Claxton AJ. Economic cost and epidemiological characteristics of patients with fibromyalgia claims. The Journal of rheumatology. 2003;30(6):1318-25.
4. Adams N, Sim J. Rehabilitation approaches in fibromyalgia. Disability and Rehabilitation. 2005;27(12):711-23.
5. Häuser W, Walitt B, Fitzcharles M-A, Sommer C. Review of pharmacological therapies in fibromyalgia syndrome. Arthritis research & therapy. 2014;16(1):201.
6. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annual review of neuroscience. 1984;7(1):309-38.
7. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. The Journal of clinical investigation. 2010;120(11):3779-87.
8. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. Current opinion in supportive and palliative care. 2014;8(2):143.
9. Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. Expert review of neurotherapeutics. 2012;12(5):577-85.
10. de la Coba P, Bruehl S, Moreno-Padilla M, Reyes del Paso GA. Responses to slowly repeated evoked pain stimuli in fibromyalgia patients: evidence of enhanced pain sensitization. Pain Medicine. 2017;18(9):1778-86.
11. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. 2005;114(1-2):295-302.
12. Mhalla A, de Andrade DC, Baudic S, Perrot S, Bouhassira D. Alteration of cortical excitability in patients with fibromyalgia. Pain. 2010;149(3):495-500.
13. Gibson S, Littlejohn G, Gorman M, Helme R, Granges G. Altered heat pain thresholds and cerebral event-related potentials following painful CO2 laser stimulation in subjects with fibromyalgia syndrome. Pain. 1994;58(2):185-93.
14. Stevens A, Batra A, Kötter I, Bartels M, Schwarz J. Both pain and EEG response to cold pressor stimulation occurs faster in fibromyalgia patients than in control subjects. Psychiatry research. 2000;97(2-3):237-47.
15. Cardinal TM, Antunes LC, Brietzke AP, Parizotti CS, Carvalho F, De Souza A, et al. Differential neuroplastic changes in fibromyalgia and depression indexed by up-regulation of motor cortex inhibition and disinhibition of the descending pain system: an exploratory study. Frontiers in human neuroscience. 2019;13.
16. Deitos A, Soldatelli MD, Dussán-Sarria JA, Souza A, da Silva Torres IL, Fregni F, et al. Novel Insights of Effects of Pregabalin on Neural Mechanisms of Intracortical Disinhibition in Physiopathology of Fibromyalgia: An Explanatory, Randomized, Double-Blind Crossover Study. Frontiers in human neuroscience. 2018;12.
17. Pujol J, López-Solà M, Ortiz H, Vilanova JC, Harrison BJ, Yücel M, et al. Mapping brain response to pain in fibromyalgia patients using temporal analysis of FMRI. PloS one. 2009;4(4):e5224.
18. Williams DA, Gracely RH. Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia. Arthritis research & therapy. 2007;8(6):224.

19. Burgmer M, Pogatzki-Zahn E, Gaubitz M, Wessoleck E, Heuft G, Pfleiderer B. Altered brain activity during pain processing in fibromyalgia. Neuroimage. 2009;44(2):502-8.
20. Schrepf A, Harper DE, Harte SE, Wang H, Ichesco E, Hampson JP, et al. Endogenous opioidergic dysregulation of pain in fibromyalgia: a PET and fMRI study. Pain. 2016;157(10):2217.
21. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis & Rheumatism. 2002;46(5):1333-43.
22. Busch AJ, Barber KA, Overend TJ, Peloso PMJ, Schachter CL. Exercise for treating fibromyalgia syndrome. Cochrane database of systematic reviews. 2007 (4).
23. Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain. 2006;122(1-2):197-209.
24. DaSilva AF, Mendonca ME, Zaghi S, Lopes M, DosSantos MF, Spierings EL, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. Headache: The Journal of Head and Face Pain. 2012;52(8):1283-95.
25. Antal A, Terney D, Kühnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. Journal of pain and symptom management. 2010;39(5):890-903.
26. Fenton BW, Palmieri PA, Boggio P, Fanning J, Fregni F. A preliminary study of transcranial direct current stimulation for the treatment of refractory chronic pelvic pain. Brain stimulation. 2009;2(2):103-7.
27. Vaseghi B, Zoghi M, Jaberzadeh S. Does anodal transcranial direct current stimulation modulate sensory perception and pain? A meta-analysis study. Clinical Neurophysiology. 2014;125(9):1847-58.
28. Fregni F, Freedman S, Pascual-Leone A. Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. The Lancet Neurology. 2007;6(2):188-91.
29. O'connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. Cochrane database of systematic reviews. 2018 (3).
30. Zhu C-E, Yu B, Zhang W, Chen W-H, Qi Q, Miao Y. Effectiveness and safety of transcranial direct current stimulation in fibromyalgia: a systematic review and meta-analysis. Journal of rehabilitation medicine. 2017;49(1):2-9.
31. Fregni F, Gimenes R, Valle AC, Ferreira MJ, Rocha RR, Natalle L, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 2006;54(12):3988-98.
32. Fagerlund AJ, Hansen OA, Aslaksen PM. Transcranial direct current stimulation as a treatment for patients with fibromyalgia: a randomized controlled trial. Pain. 2015;156(1):62-71.
33. Carvalho F, Brietzke AP, Gasparin A, dos Santos FP, Vercelino R, Ballester RF, et al. Home-based transcranial direct current stimulation device development: an updated protocol used at home in healthy subjects and fibromyalgia patients. JoVE (Journal of Visualized Experiments). 2018 (137):e57614.
34. Brunoni AR, Valiengo L, Baccaro A, Zanao TA, de Oliveira JF, Goulart A, et al. The sertraline vs electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA psychiatry. 2013;70(4):383-91.
35. Hazime F, Baptista A, de Freitas D, Monteiro R, Maretto R, Hasue R, et al. Treating low back pain with combined cerebral and peripheral electrical stimulation: A randomized, double-blind, factorial clinical trial. European Journal of Pain. 2017;21(7):1132-43.
36. Viana R, Laurentino G, Souza R, Fonseca J, Silva Filho E, Dias S, et al. Effects of the addition of transcranial direct current stimulation to virtual reality therapy after stroke: a pilot randomized controlled trial. NeuroRehabilitation. 2014;34(3):437-46.

37. Mendonca ME, Simis M, Grecco LC, Battistella LR, Baptista AF, Fregni F. Transcranial direct current stimulation combined with aerobic exercise to optimize analgesic responses in fibromyalgia: a randomized placebo-controlled clinical trial. Frontiers in human neuroscience. 2016;10:68.
38. Ellingson LD, Stegner AJ, Schwabacher IJ, Koltyn KF, Cook DB. Exercise Strengthens Central Nervous System Modulation of Pain in Fibromyalgia. Brain sciences. 2016 Feb 26;6(1). PubMed PMID: 26927193. PMCID: PMC4810178. Epub 2016/03/02. eng.
39. Theadom A, Cropley M, Smith HE, Feigin VL, McPherson K. Mind and body therapy for fibromyalgia. The Cochrane database of systematic reviews. 2015 Apr 9(4):Cd001980. PubMed PMID: 25856658. Epub 2015/04/10. eng.
40. Castillo-Saavedra L, Gebodh N, Bikson M, Diaz-Cruz C, Brandao R, Coutinho L, et al. Clinically Effective Treatment of Fibromyalgia Pain With High-Definition Transcranial Direct Current Stimulation: Phase II Open-Label Dose Optimization. The journal of pain : official journal of the American Pain Society. 2016 Jan;17(1):14-26. PubMed PMID: 26456677. PMCID: PMC5777157. Epub 2015/10/13. eng.
41. Villamar MF, Wivatvongvana P, Patumanond J, Bikson M, Truong DQ, Datta A, et al. Focal modulation of the primary motor cortex in fibromyalgia using 4x1-ring high-definition transcranial direct current stimulation (HD-tDCS): immediate and delayed analgesic effects of cathodal and anodal stimulation. The journal of pain : official journal of the American Pain Society. 2013 Apr;14(4):371-83. PubMed PMID: 23415877. Epub 2013/02/19. eng.
42. Borckardt JJ, Bikson M, Frohman H, Reeves ST, Datta A, Bansal V, et al. A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. The journal of pain : official journal of the American Pain Society. 2012 Feb;13(2):112-20. PubMed PMID: 22104190. Epub 2011/11/23. eng.
43. ACSM. ACSM's Guidelines for Exercise Testing and Prescription. 9th ed: Lippincott Williams & Wilkins; 2015.
44. Stephens S, Feldman BM, Bradley N, Schneiderman J, Wright V, Singh-Grewal D, et al. Feasibility and effectiveness of an aerobic exercise program in children with fibromyalgia: results of a randomized controlled pilot trial. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2008;59(10):1399-406.
45. Oliveira N, dos Santos Sabbag L, de Sa Pinto A, Borges C, Lima F. Aerobic exercise is safe and effective in systemic sclerosis. International journal of sports medicine. 2009;30(10):728-32.
46. Gill TM, DiPietro L, Krumholz HM. Role of exercise stress testing and safety monitoring for older persons starting an exercise program. Jama. 2000;284(3):342-9.
47. Roveda F, Middlekauff HR, Rondon MUP, Reis SF, Souza M, Nastari L, et al. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. Journal of the American College of Cardiology. 2003;42(5):854-60.
48. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews. 2017 (4).
49. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of physiology. 2000;527(3):633-9.
50. Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clinical neurophysiology. 2006;117(4):845-50.
51. Potvin S, Marchand S. Pain facilitation and pain inhibition during conditioned pain modulation in fibromyalgia and in healthy controls. Pain. 2016;157(8):1704-10.
52. Granot M, Weissman-Fogel I, Crispel Y, Pud D, Granovsky Y, Sprecher E, et al. Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: do conditioning stimulus painfulness, gender and personality variables matter? Pain. 2008;136(1-2):142-9.

53. Nirl RR, Granovskyl Y, Yarnitskyl D, Sprecherl E, Granotl M. A psychophysical study of endogenous analgesia: the role of the conditioning pain in the induction and magnitude of conditioned pain modulation. European journal of pain. 2011;15(5):491-7.
54. Bosma RL, Mojarad EA, Leung L, Pukall C, Staud R, Stroman PW. F MRI of spinal and supra-spinal correlates of temporal pain summation in fibromyalgia patients. Human brain mapping. 2016;37(4):1349-60.
55. Craggs JG, Staud R, Robinson ME, Perlstein WM, Price DD. Effective connectivity among brain regions associated with slow temporal summation of C-fiber-evoked pain in fibromyalgia patients and healthy controls. The Journal of Pain. 2012;13(4):390-400.
56. Staud R, Weyl EE, Riley III JL, Fillingim RB. Slow temporal summation of pain for assessment of central pain sensitivity and clinical pain of fibromyalgia patients. PloS one. 2014;9(2):e89086.
57. Vierck Jr CJ, Cannon RL, Fry G, Maixner W, Whitsel BL. Characteristics of temporal summation of second pain sensations elicited by brief contact of glabrous skin by a preheated thermode. Journal of neurophysiology. 1997;78(2):992-1002.
58. Williams JA, Pascual-Leone A, Fregni F. Interhemispheric modulation induced by cortical stimulation and motor training. Physical therapy. 2010;90(3):398-410.
59. Rossini PM, Micera S, Benvenuto A, Carpaneto J, Cavallo G, Citi L, et al. Double nerve intraneural interface implant on a human amputee for robotic hand control. Clinical neurophysiology. 2010;121(5):777-83.
60. Li H, Huang G, Lin Q, Zhao JL, Lo WA, Mao YR, et al. Combining Movement-Related Cortical Potentials and Event-Related Desynchronization to Study Movement Preparation and Execution. Frontiers in neurology. 2018;9:822. PubMed PMID: 30344504. PMCID: PMC6182054. Epub 2018/10/23. eng.
61. Duann JR, Chiou JC. A Comparison of Independent Event-Related Desynchronization Responses in Motor-Related Brain Areas to Movement Execution, Movement Imagery, and Movement Observation. PLoS One. 2016;11(9):e0162546. PubMed PMID: 27636359. PMCID: PMC5026344. Epub 2016/09/17. eng.
62. Neuper C, Wortz M, Pfurtscheller G. ERD/ERS patterns reflecting sensorimotor activation and deactivation. Progress in brain research. 2006;159:211-22. PubMed PMID: 17071233. Epub 2006/10/31. eng.
63. Nuwer MR, Lehmann D, Silva FLd, Matsuoka S, Sutherling W, Vibert J-F. IFCN guidelines for topographic and frequency analysis of EEGs and EPs. Report of an IFCN committee. Electroencephalography and clinical Neurophysiology. 1994;91(1):1-5.
64. Liu C, Wang H, Pu H, Zhang Y, Zou L, editors. EEG feature extraction and pattern recognition during right and left hands motor imagery in brain-computer interface. 2012 5th International Conference on BioMedical Engineering and Informatics; 2012: IEEE.
65. Ribeiro H, Sesterhenn RB, Souza A, Souza AC, Alves M, Machado JC, et al. Preoperative transcranial direct current stimulation: Exploration of a novel strategy to enhance neuroplasticity before surgery to control postoperative pain. A randomized sham-controlled study. PLoS One. 2017;12(11):e0187013. PubMed PMID: 29190741. PMCID: PMC5708693. Epub 2017/12/01. eng.
66. Braulio G, Passos SC, Leite F, Schwertner A, Stefani LC, Palmer ACS, et al. Effects of Transcranial Direct Current Stimulation Block Remifentanil-Induced Hyperalgesia: A Randomized, Double-Blind Clinical Trial. Frontiers in pharmacology. 2018;9:94. PubMed PMID: 29515438. PMCID: PMC5825908. Epub 2018/03/09. eng.
67. Flood A, Waddington G, Keegan RJ, Thompson KG, Cathcart S. The effects of elevated pain inhibition on endurance exercise performance. PeerJ. 2017;5:e3028. PubMed PMID: 28265507. PMCID: PMC5337081. Epub 2017/03/08. eng.

68. Flood A, Waddington G, Cathcart S. High-Definition Transcranial Direct Current Stimulation Enhances Conditioned Pain Modulation in Healthy Volunteers: A Randomized Trial. The journal of pain : official journal of the American Pain Society. 2016 May;17(5):600-5. PubMed PMID: 26844419. Epub 2016/02/05. eng.

69. da Silva NR, Laste G, Deitos A, Stefani LC, Cambraia-Canto G, Torres IL, et al. Combined neuromodulatory interventions in acute experimental pain: assessment of melatonin and non-invasive brain stimulation. Frontiers in behavioral neuroscience. 2015;9:77. PubMed PMID: 25873871. PMCID: PMC4379934. Epub 2015/04/16. eng.

70. Meeus M, Hermans L, Ickmans K, Struyf F, Van Cauwenbergh D, Bronckaerts L, et al. Endogenous pain modulation in response to exercise in patients with rheumatoid arthritis, patients with chronic fatigue syndrome and comorbid fibromyalgia, and healthy controls: a double-blind randomized controlled trial. Pain practice : the official journal of World Institute of Pain. 2015 Feb;15(2):98-106. PubMed PMID: 24528544. Epub 2014/02/18. eng.

71. Garcia-Hermoso A, Saavedra JM, Escalante Y. Effects of exercise on functional aerobic capacity in adults with fibromyalgia syndrome: A systematic review of randomized controlled trials. Journal of back and musculoskeletal rehabilitation. 2015;28(4):609-19. PubMed PMID: 25408119. Epub 2014/11/20. eng.

72. Bidonde J, Busch AJ, Schachter CL, Overend TJ, Kim SY, Goes SM, et al. Aerobic exercise training for adults with fibromyalgia. The Cochrane database of systematic reviews. 2017 Jun 21;6:Cd012700. PubMed PMID: 28636204. PMCID: PMC6481524. Epub 2017/06/22. eng.

73. Wang C, Schmid CH, Fielding RA, Harvey WF, Reid KF, Price LL, et al. Effect of tai chi versus aerobic exercise for fibromyalgia: comparative effectiveness randomized controlled trial. BMJ (Clinical research ed). 2018 Mar 21;360:k851. PubMed PMID: 29563100. PMCID: PMC5861462 at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from National Center for Complementary and Integrative Health at the National Institutes of Health in the US for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. Epub 2018/03/23. eng.

74. Marske C, Bernard N, Palacios A, Wheeler C, Preiss B, Brown M, et al. Fibromyalgia with Gabapentin and Osteopathic Manipulative Medicine: A Pilot Study. Journal of alternative and complementary medicine (New York, NY). 2018 Apr;24(4):395-402. PubMed PMID: 29298077. Epub 2018/01/04. eng.

75. Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity on perceived symptoms and physical function in adults with fibromyalgia: results of a randomized trial. Arthritis Res Ther. 2010;12(2):R55. PubMed PMID: 20353551. PMCID: PMC2888205. Epub 2010/04/01. eng.

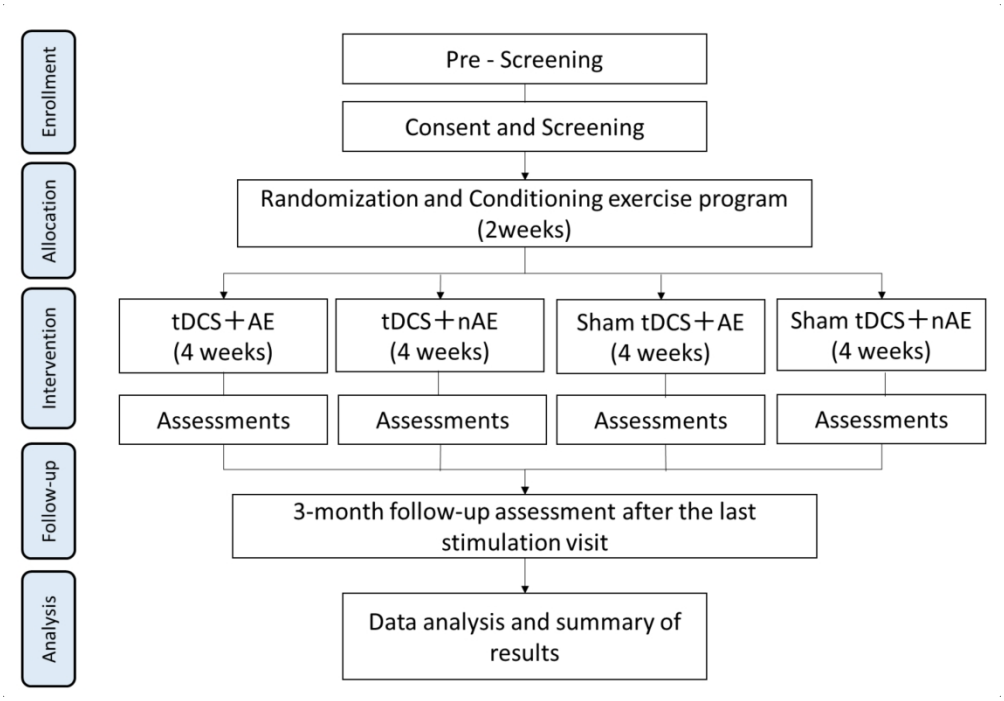
76. Valle A, Roizenblatt S, Botte S, Zaghi S, Riberto M, Tufik S, et al. Efficacy of anodal transcranial direct current stimulation (tDCS) for the treatment of fibromyalgia: results of a randomized, sham-controlled longitudinal clinical trial. Journal of pain management. 2009;2(3):353-61. PubMed PMID: 21170277. PMCID: PMC3002117. Epub 2009/01/01. eng.

77. Möller H-J, Müller H, Borison RL, Schooler NR, Chouinard G. A path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in schizophrenic patients. European archives of psychiatry and clinical neuroscience. 1995;245(1):45-9.

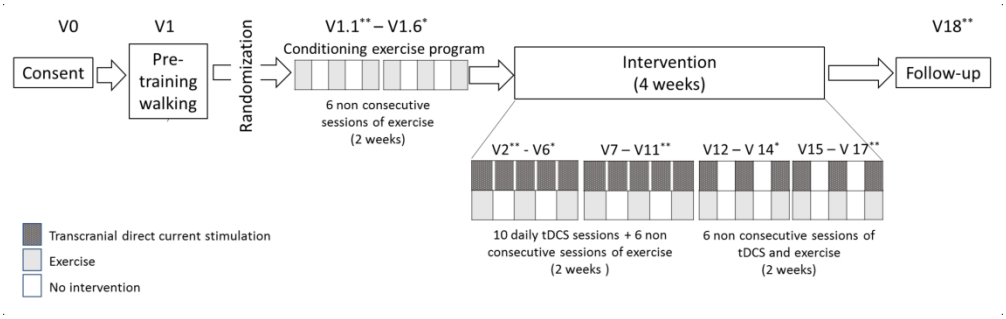
Figure Legends:

Figure 1 Flow chart of the study based on CONSORT criteria.

Figure 2 Schematic view of the timeline



Flow chart of the study based on CONSORT criteria.



Schematic view of the timeline

Trial registration dataset	
Data Category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03371225
Date of registration in primary registry	December 13, 2017
Secondary identifying numbers	2017P002524
Source of monetary or material support	National Institutes of Health (NIH)
Primary sponsor	National Institutes of Health (NIH)
Contact for public queries	Felipe Fregni, MD, PhD, MPh, MMSc
Contact for scientific queries	Felipe Fregni, MD, PhD, MPh, MMSc
Public title	Optimized tDCS for fibromyalgia: targeting the endogenous pain control system
Scientific title	Optimized tDCS for fibromyalgia – targeting the endogenous pain control system: A randomized, double-blind, factorial clinical trial protocol
Countries of recruitment	United States
Health condition(s) or problem(s) studies	Fibromyalgia
Interventions	Device: Active tDCS; Procedure: Active Exercise; Device: Sham tDCS; Procedure: Sham Exercise
Key inclusion and exclusion criteria	**Inclusion criteria:** 1) 18-65 years; 2) Diagnosis of FM pain according to the ACR 2010 criteria; 3) Pain resistant to common analgesics and medications for chronic pain; 4) Must have the ability to feel sensation by Von-Frey fiber on the forearm; 5) Able to provide informed consent to participate in the study. **Exclusion criteria:** 1) Clinically significant or unstable medical or psychiatric disorder; 2) History of substance abuse within the past 6 months as self-reported; 3) Previous significant neurological history; 4) Previous neurosurgical procedure with craniotomy; 5) Severe depression; 6) Pregnancy; 7) Current opiate use in large doses; 8) increased risk for exercise

Study type	Interventional
	Randomized, double-blind, factorial clinical trial
Date of first enrolment	May 2019
Target sample size	148
Recruitment status	Recruiting
Primary outcome(s)	Conditioned Pain Modulation (CPM); Temporal Slow Pain Summation (TSPS)
Key secondary outcomes	Intracortical inhibition assessed by TMS; thalamocortical dysrhythmia (TCD) and event related desynchronization (ERD) assessed by EEG; Average pain intensity as assessed by Modified Brief Pain Inventory (BPI); Revised Fibromyalgia Impact Questionnaire (FIQ-R); Quality of life assessed by Quality of Life Scale (QoLS), Patient Reported Outcomes Measurement Information System (PROMIS); Pittsburgh Sleep Quality Index (PSQI) and Beck Depression Inventory (BDI).

Protocol Version:
Issue date: 05/16/2019
Protocol amendment number: 08

Revision Chronology
18/01/2018: Original submission
08/23/2018: Amendment 01- Primary reason for amendment: clarification of inclusion/exclusion criteria
11/02/2018: Amendment 04 - Primary reason for amendment: clarification of TMS protocol
16/05/2019: Amendment 08- Primary reason for amendment: clarification of CPM and TSPS procedures

All other Amendments (01, 03, 05, 06, 07) were related to changes in study staff. Any further amendments will follow Partners Healthcare institutional policies.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	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	11
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a. Supplementary file
Protocol version	#3	Date and version identifier	n/a. Supplementary file
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	11

contributorship				
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a. NIH funded	
Roles and responsibilities: sponsor and funder	#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	n/a. NIH funded	
Roles and responsibilities: committees	#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)	n/a- PI oversees the study	
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
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators		3
Objectives	#7	Specific objectives or hypotheses		3
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, non-inferiority, exploratory)		4
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	4
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)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#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)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	7
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)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions	9

		supporting any sample size calculations		
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size		4
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		4
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		4
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions		4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how		4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a. We do not anticipate circumstances that would require emergency unblinding	
Methods: Data collection, management, and analysis				
Data collection plan	#18a	Plans for assessment and collection of outcome,		10

		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	
Data collection plan: retention	#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	10
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	10
Statistics: outcomes	#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	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#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)	11
Methods: Monitoring			
Data monitoring: formal committee	#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,	11

		an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#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	n/a. No interim analyses will be performed
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	6
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
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)	n/a. Supplementary file
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	2

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
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	n/a
Dissemination policy: trial results	#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	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	There will be no use of professional writers. Authorship will be decided among study personnel with intellectual contributions.
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Informed consent follows Partners Healthcare institutional policies
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	n/a. There will be no collection of biological specimens/a. There will be no collection of biological specimens.

Notes:

- 2b: n/a. Supplementary file
- 3: n/a. Supplementary file

- 5b: n/a. NIH funded
- 5c: n/a. NIH funded
- 5d: n/a- PI oversees the study
- 17b: n/a. We do not anticipate circumstances that would require emergency unblinding
- 21b: n/a. No interim analyses will be performed
- 25: n/a. Supplementary file
- 31b: There will be no use of professional writers. Authorship will be decided among study personnel with intellectual contributions.
- 32: Informed consent follows Partners Healthcare institutional policies
- 33: n/a. There will be no collection of biological specimens/a. There will be no collection of biological specimens. The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 01. July 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai