Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Protocol Number: H-47781
Status: Approved
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Approval Period: 12/19/2022 - 12/18/2023

Section Aa: Title & PI

A1. Main Title

EFFECTIVENESS OF LOWER EXTREMITY ELECTRICAL STIMULATION THERAPY IN THE TREATMENT OF LOWER EXTREMITY CRITICAL ILLNESS MYOPATHY AND NEUROPATHY IN PATIENTS WITH SEVERE COVID-19

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A3a. Financial Conflict of Interest

Does any member of study personnel (Investigator (including investigatorâ€™s spouse and/or dependent children)) that are involved in the design, conduct, or reporting of the research have a Significant Financial Interest (SFI) that would reasonably appear to be affected by the research for which funding is sought and/or associated with an entity/business that would reasonably appear to be affected by the research?

No

Section Ab: General Information

A4. Co-Investigators

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A5. Funding Source:

Baylor College of Medicine (Internal Funding Only)

A6a. Institution(s) where work will be performed:

BCM: Baylor College of Medicine
Baylor St. Luke's Medical Center (BSLMC)

A6b. Research conducted outside of the United States:

Country:
Facility/Institution:
Contact/Investigator:
Phone Number:

If documentation of assurances has not been sent to the Office of Research, please explain:

A7. Research Category:

A8. Therapeutic Intent

Does this trial have therapeutic intent?
Yes

A9. ClinicalTrials.gov Registration

Does this protocol/trial require registration on ClinicalTrials.gov due to it: meeting the definition of an Applicable Clinical Trial, being required under the terms and conditions of an award, or being proposed to be published in ICMJE journals?
Yes

Who will be responsible for registering and maintaining the registration of this Applicable Clinical Trial?
The BCM PI will register the trial because either:

- the trial is BCM PI-initiated,
- BCM is the lead site of this multicenter trial, or,
- the industry sponsor has instructed the BCM PI to register the trial, or,
- registration of this trail is required as a term and condition of the reward by the funding agency.

ClinicalTrials.gov Identifier:
NCT

Section B: Exempt Request

B. Exempt From IRB Review

Not Applicable

Section C: Background Information

Critically ill patients often suffer from hospital acquired weakness. This condition may originate from Neurogenic (critical illness Polyneuropathy or CIP) or Myogenic (critical illness Myopathy or CIM) disturbances, or a combination of both (critical illness Neuro-Myopathy or CINM). Moreover, prolonged hospital stay has been associated with pronounced loss of muscle mass that can exceed 10% over the 1st week, which leads to functional impairment and complications post-hospital discharge. Prevalence of hospital-acquired weakness varies widely depending on patient population and risk factors, assessment period, diagnosis method, and patients pre-hospital functional status (age-related frailty).

Unfortunately, hospital-acquired weakness is highly prevalent among COVID-19 patients, who require paralytics for an extended period of time in order to maintain oxygenation. The prolonged use of these agents lead to long-term inhibition of the Acetylcholine receptors of Neuromuscular junctions. All COVID-19 ventilated patients at our institution have been on paralytics for at least 48 hours, and most of these patients receive concomitant Glucocorticoid therapy. Together Glucocorticoids and paralytics, lead to Myosin depletion and muscle atrophy. This combination has shown to be a risk factor for CINM. In a recent JAMA study on 5700 COVID-19 patients performed in NYC, 72% of the ventilated patients remained in the hospital, and only 3% of this population have been discharged. We believe that the major reason for this is the inability to wean from the ventilator and to rehabilitate due to Neuro-Myopathy.

A recent systematic review suggested the major pathways involved in CINM. These major pathways include muscle disuse due to prolonged immobilization, inflammation, impaired perfusion and oxygen delivery, and hyperglycemia. All these factors might be magnified among COVID-19 patients. Additional to muscle atrophy, a hyper-inflammatory systemic state and coagulation disorders induced by the COVID-19 virus, poor blood oxygen saturation, and poor perfusion to lower extremities are other important risk factors to be aware in these patients. As described above, this type of work may allow physicians to provide more personalized care and evaluate their interventions with a practical test.

Muscle weakness and fatigue impede patients¿ capacity to exercise, and are known to delay extubation, extend length of stay in hospital, and delay patients to achieve independent mobility. The goal of E-stim in advanced disease states is to prevent or reverse skeletal muscle wasting for persons who are not able to exercise. Conditions include advanced periods of mechanical ventilation.

A recent review including 27 papers regarding E-Stim for critical illness in hospital patients revealed a summary of E-stim characteristics which have shown to benefit this specific population. Characteristics include: a) electrode placement in lower extremity muscle groups bilaterally, hams and calf muscles; b) position for E-stim in hospital patients should be supine; and c) session frequency is effective at 5¿7 d/wk or daily until extubation or D/C from hospital. In this summary, Nussbau, et al reported a series of measurements to demonstrate the efficacy of E-stim therapy such as: thigh circumference, strength of lower extremity muscles (isometric or isotonic dynamometry, MRC score), and quality of life questionnaires. The majority of these studies selected parameters to minimize muscle fatigue. They concluded that E-stim preserves muscle strength and muscle mass, and reduces rate of muscle degradation. Also, it facilitates maintenance of functional capacity. Others have suggested that the benefit of E-stim was related to neural adaptations.

Additionally, our previous studies demonstrated that daily use of EE therapy effectively improves limb perfusion, oxygen delivery, Neuropathy, motor capacity (e.g., gait and balance), and mobility (e.g., daily number of steps). Armed with these preliminary studies, we proposed this current study to examine the effect of daily use EE therapy in critically ill COVID-19 patients. Our fundamental hypothesis is that EE therapy is effective to maintain the activation of lower extremity muscles and improve perfusion and oxygen delivery, thus preventing or reversing CINM due to prolonged hospital stay.

This is the previous study that our protocol mentions:

Thakral G, Lafontaine J, Najafi B, et al. Electrical stimulation to accelerate wound healing. Diabetic foot & ankle. 2013;4. More references below: Reid B, Zhao M. The Electrical Response to Injury: Molecular Mechanisms and Wound Healing. Advances in wound care. 2014;3(2):184-201 Ud-Din S, Bayat A. Electrical Stimulation and Cutaneous Wound Healing: A Review of Clinical Evidence. Healthcare. 2014;2(4):445-467 Ashrafi M, Alonso-Rasgado T, Baguneid M, et al. The efficacy of electrical stimulation in lower extremity cutaneous wound healing: A systematic review. Experimental dermatology. 2017;26(2):171-178. Rachel L-C Kwan GL-YC, Sinfia K-S Vong & Sing K Lo. Electrophysical therapy for managing diabetic foot ulcers: a systematic review. 10. 2013(121-131). Bai H, McCaig CD, Forrester JV, et al. DC electric fields induce distinct Preangiogenic responses in Microvascular and macrovascular cells. Arteriosclerosis, thrombosis, and vascular biology. 2004;24(7):1234-1239. Kloth LC. Electrical stimulation for wound healing: a review of evidence from in vitro studies, animal experiments, and clinical trials. The international journal of lower extremity wounds. 2005;4(1):23-44.

Electrical stimulation device is used for pain management, for this study it will be used as an investigational device to test the treatment/ prevention of Myopathy an Neuropathy in the hospital (inpatient setting).

Section D: Purpose and Objectives

This study is divided in two phases.

Phase I (preventive): Unfortunately, hospital-acquired weakness is highly prevalent among COVID-19 hospitalized patients, who often require prolonged bed-rest or paralytics for an extended period of time in order to maintain oxygenation. Prolonged bed rest has been associated with pronounced loss of muscle mass that can exceed 10% over the 1st week, which leads to functional impairment and complications post-hospital discharge. Physical therapy and in-hospital mobility program may reduce the incident of hospital-acquired weakness, but they are often impractical for COVID-19 patients. In particular, conventional mobility programs are challenging for those who are being treated in an intensive Care Unit. The purpose of this phase of study is to test feasibility and proof-of-concept effectiveness of lower extremity electrical stimulation (EE) therapy to prevent muscular complications of COVID-19 including hospital-acquired weakness and neuropathy.

Phase II (recovery): Moreover, we also propose to examine the effectiveness of daily use of electrical stimulation therapy to recover from the long-term neuromuscular side effects of prolonged immobilization in patients who were bedbound due to COVID-19. These effects include lower extremity critical illness myopathy and neuropathy. Lengthened periods of immobilization decreases muscle activity provoking atrophy, weakness, and pain. We hypothesize that electrical stimulation will help to increase muscle fiber activation and nerve conductivity, thus, help in recovery of the neuromuscular condition.

Section E: Protocol Risks/Subjects

E1. Risk Category

Category 1: Research not involving greater than minimum risk.

E2. Subjects

Gender:
Both

Age:
Adult (18-64 yrs), Geriatric (65+ yrs)

Ethnicity:
All Ethnicities

Primary Language:
English

Groups to be recruited will include:
Patients

Which if any of the following vulnerable populations will be recruited as subjects?
Cognitively impaired

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

Due to no visitation, the consent will be done over the phone by the physician with a legal representative of the patient. Two nurses will be present during the call and the consenting will be done by the physician following current consenting procedures with other ongoing studies in the hospital. This study has minimal risks for the patient, all notes will be added to the consent form based on the call. If patient is able to give verbal consent will be singed physically.

For patients who lack the capacity to consent, the investigator/designee may explain the study to the legally authorized representative by phone. The discussion will be documented in the subject's medical record or research chart. Two copies of the unsigned consent form will be sent to the subject/legal representative with instructions for completion of the signature page and assent (if applicable). Signatures will be obtained according to standard Baylor IRB regulations. The subject will be told to keep one form and returned the other to the investigator by mail, email, or fax. The Baylor Investigator/designee will sign the consent form when returned from the subject. The signed consent form will be maintained in research records.

E3. Pregnant woman/fetus

Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E4. Neonates

Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?
No

E5. Children

Will children be enrolled in the research?

No

Section F: Design/Procedure

F1. Design

Select one category that most adequately describes your research:

c) Pilot

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.

Phase I: 20 subjects with COVID-19 infection that are being treated in the hospital. This means that this patient population is positive to COVID-19 and have been admitted with no more than 48 hours to the hospital due to severe infection. In some cases, the patients will not able to consent at the time of enrollment. This determines a high grade of severity of illness. Therefore, a family member/legal representative will be contacted via telephone for consenting. Participants will be randomized to intervention (IG) or control group (CG). The entire cohort will receive daily EE in lower extremity (e.g. Gastronemius, tibial anterior muscle) up to 1 hour. EE therapy will be provided using portable device. The EE device will be functional for IG and non-functional for CG. The duration of the study will be 2 weeks or until patient discharge, whichever comes first. The primary outcomes include between group difference and change from the baseline in muscle endurance, muscle strength, lower extremity tissue oxygen saturation, neuropathy, and muscle atrophy. Outcomes will be assessed at baseline, time of discharge or 2 weeks, whichever comes first. Due to the condition of the patient we are looking to reduce the interaction with staff, the device will be placed with no additional requirements. Physical therapy targets other physical performances, this device is aimed to improve blood flow, tissue perfusion and muscle activation while the patient is non-responsive to physical activities.

Phase II: 20 additional subjects coming to the COVID-19 clinic at Baylor College of Medicine for treatment of long-term neuromuscular complications due to severe COVID-19 infection. Patients will begin the study after indication of muscle weakness, muscle atrophy, fatigue, or neuromyopathy due to prolonged immobilization (i.e. at home or in the hospital) for COVID-19. This assessment can be performed by a critical care and pulmonary specialist at the BCM COVID-19 Clinic. This is a proof of concept randomized control trial (RCT) study for recovery. The entire cohort will receive daily, at-home electrical stimulation in the lower extremities (e.g. gastrocnemius, tibial anterior muscle) for up to 1 hour to aid in recovery from neuromyopathy complications due to prolonged immobilization. Participants will be randomized to intervention (IG) or control group (CG). EE therapy will be provided using a portable EE device. The EE device will be functional for IG and non-functional for CG. The primary outcomes include between group difference and change from the baseline in muscle endurance, muscle strength, lower extremity tissue oxygen saturation, neuropathy, and muscle atrophy. The patients will take the device home up to 4 weeks and will be screened once a week at Baylor College of Medicine McNair Campus for neuromuscular evaluation. The control group will be unblinded after the 4 weeks are completed with the option of extending to 4 additional weeks by switching to an active device.

Inclusion Criteria:

Phase I: Age: Adults age 18 years or older Disease status: COVID-19 test positive Critically ill requiring care in the hospital.

Phase II: Age: Adults age 18 years or older Patients must have been previously bedbound or immobilized due to COVID-19 infection Patients with muscle pain, muscle weakness, muscle atrophy, and/or neuromyopathy in the lower extremities Patients will have to be alert and conscious to sign the consent form.

Exclusion Criteria:

Subject has a demand-type cardiac pacemaker, implanted defibrillator or other implanted electronic device Active wound infection Below the knee amputations Based on the clinicians decision whether the patient is eligible for the study.

F2. Procedure

Phase I:

Aim1 (to understand mechanism of action): Examine immediate benefit of lower extremity EE to improve venous return flow, tissue oxygenation, and muscle activation (short term benefit). In this study, we will recruit a convenient sample of 20 hospital patients diagnosed with COVID-19 (short-term benefit).

Optional: Subjects will be assessed using Doppler ultrasound and near infrared imaging (Kent Imaging System) at pre-, 30min, 60min, and 30min post-treatment (after stopping of EE device). Lower extremity muscle activation will be assessed by using sEMG (electromyography).

Patients will begin the study after being admitted to the hospital no more than 48 hours.

Aim 2 (to examine effectiveness): Examine effectiveness of daily use of EE to treat CINM, and other associated major adverse events (MAE) including deep vein thrombosis (DVT), cardiovascular events, and death. Participants will receive standard of care plus adjunctive daily EE therapy using an FDA approved bio-electric stimulation technology (BEST) platform (Tennant Biomodulator® PRO, AVAZZIA, Inc) during the entire length of stay in hospital. The device will be provided by the research staff.

We will assess incidence of neuropathy and myopathy during hospital discharge or 2 weeks, whichever comes first. Neuropathy severity will be quantified using vibratory perception threshold (VPT) test. Myopathy will be assessed by measuring changes in calf muscle circumstance, weight change from pre-hospital admission, and sEMG. In addition, we will determine weakness using foot dynamometer and a validated frailty meter. Length of hospital stay and MAE (documented via electronic health record) will be tracked for planning of future studies. Both extremities will have all measurements and 1 hour electrical stimulation therapy at baseline. Daily treatment will performed up to 3 times per day, but no more than 1 hour in total.

Daily electrical stimulation will be administered by a nurse/staff involved in the hospital care. A chart will be signed to register each therapy performed and will include a log of day and time of device application.

Both electrical stimulation and EMG devices will have disposable pads, after usage they will be discarded. For the Devices they will be placed inside a plastic bag that will be disposed inside the room before exiting and sanitized (wipes) based upon hospital protocols.

The researchers will take digital photographs /videos throughout the study. This is done using a special camera for tissue oxygen detection and visual images. This method is non invasive and does not cause any harm to the patient. **We will blur the face out in the photographs/videos. We will only use videos and photos for scientific presentations or scientific publications.

Phase II:

Patients will begin the study after incidence of muscle loss, muscle weakness, muscle pain, or neuromyopathy due to prolonged immobilization for COVID-19. This assessment will be performed by a critical care and pulmonary specialist at the BCM COVID-19 Clinic.

The protocol will consist of 4 weeks of lower-extremity electrical stimulation. This modality will consist of home-based therapy, meaning that the patient will take the device home and attend the clinic once a week for screening and assessment of therapy.

The protocol will be performed as the following description: This trial will have 20 patients divided in two groups. Group 1 (intervention, n=10): Will receive an active Tennant Biomodulator. Patients assigned the active device (active group; Group 1) at their initial visit (baseline) will only have 4 weeks of study participation (which includes 5 visits: Baseline (week 0), Visit 1 (Week 1 of at-home therapy), Visit 2 (Week 2 of at-home therapy), Visit 3 (Week 3 of at-home therapy), Visit 4 (Week 4 of at-home therapy). After 4 weeks, the patients will turn back the electrical stimulation device to the research staff.

Group 2 (control, n=10): Will receive an inactive Tennant Biomodulator for 4 weeks. The control group will have the option to receive an active device after their 4 weeks visit. Should they agree, they would receive at-home therapy for another 4 weeks and come to the clinic for up to two additional visits for assessment. If the subject agrees to receive the active device at the 4th week visit (visit 4), then they will only be required to attend the clinic for one more visit (visit 5). For subjects in this group that were previously enrolled (i.e. Visit 4 completed), they will be contacted to be unblinded and confirm agreement/reconsent to have another 4weeks of study participation with an active device. They will have 2 additional visits (visit 5 and Visit 6). Visit 5 will consist of the same procedures and one hour of stimulation than visit 4, and the subject will receive an active device to take for additional 4 weeks and come back to the clinic for a final assessment (Visit 6). Visit 6 will consist of the same procedures and one hour of stimulation as visit 4. The subject will return the active device at their last visit (either Visit 5 or Visit 6 depending on the conditions listed above).

Group 2 will consist up to 7 visits total with possible phone calls in between. The patient will be compensated $50 per in-person, clinic visit (total $350), with free parking. Payment will only be available for subjects who participate in Part II.

During Visit 1, Visit 2, Visit 3, the the research staff will turn the Tennant Biomodulator PRO® on for 5 minutes and measure any changes in muscle strength, endurance, and blood flow after the therapy.

During Baseline, Visit 4, Visit 5, Visit 6, the research staff will turn the Tennant Biomodulator PRO® on for one hour and measure any changes in muscle strength, endurance, and blood flow after the therapy. Once the Baseline is over, the patient will take the Tennat Biomodulator® home and will be instructed to turn it on for one hour every day for four weeks.

Any study visits may include the following assessments in addition to electrical stimulation: 1) Questionnaires (pain, weakness, sleep, quality of life, frailty, depression, life and space, beck anxiety scale, Katz-daily living, fatigue) 2) Musculoskeletal assessments (non-invasive surface electromyography, vibration perception threshold, leg circumference measurement, ankle strength test) 3) Vascular assessments (non-invasive Near infra-red spectroscopy)

Optional measurements will also be collected to assess subject gait, balance, upper extremity strength, frailty, physical

activity, and oxygen levels (with pulse oximetry).

Gait assessment: Gait performance will be assessed using a validated body worn sensors (LegSys, Biosensics LLC, USA). The device uses five sensor modules respectively attached to right and left anterior shins, right and left anterior thighs, and posteriorly to the lower back. Based on the subject's height and using a two-link inverse pendulum model the following spatio-temporal gait parameters will be estimated: velocity, stride length, stride time, double support, single support, stride-to-stride variability, and gait initiation. In addition, the center of mass (COM) range of motion during walking will be calculated by using the data from the sensor attached to lower-back. Gait will be assessed over a distance of 20 meters under 2 conditions: (1) walking at habitual speed (2) walking at maximum speed (fast walking).

Balance assessment: Balance will be quantified using validated body worn sensors (BalanSens, Biosensics LLC, USA). The system measures ankle and hip motion in three dimensions (3D), 2D COM sway as well as RCI in ML and AP directions. Balance will be assessed according to Romberg protocol during eyes-open and eyes-closed condition during double, semi-tandem, and full tandem stances. For those patients who may not be able to do gait and balance test, we will use alternative upper extremity test, which according to our previous studies provide similar results as gait bit do not require subject to walk. (See Attachment)

Upper Extremity Frailty Test: Investigators will measure arm motion from each participant by implementing validated wearable inertial sensors (e.g. accelerometer, gyroscope) such as LegSys (Biosensics LLC, MA, USA), Frailty Meter (Biosensics LLC, MA, USA), or BioStamp (MC10, MA, USA). These inertial sensors will assess respectively kinematic of upper extremities (e.g., arm and shoulder) motion as well as joint coordination. We will be used at least 1 sensor attached on wrist to capture arm motion.

Physical Activity Monitoring: The subject will be given a wearable device (PAMSys) or a smart watch, that will be measuring several parameters including number of steps taken, duration of sitting, standing, walking and lying, time taken and number of transitions from sit to stand, and walking speed for 48 hours. At the end of the specific visit, the subject will be given the device, if they are given PAMSys it will be attached to pendant to wear around the neck, otherwise they may wear the smart watch on their wrist. Investigators will provide a pre-paid envelope where the subject may place the device and send back it to the investigating team.

Oxygen Level Assessment: Oxygen saturation will be measured using a pulse oximeter.

The supervision of this study will be by pulmonary care specialists, and the location will be at Baylor College of Medicine McNair Campus.

Section G: Sample Size/Data Analysis

G1. Sample Size

How many subjects (or specimens, or charts) will be used in this study?

Local: 40 Worldwide: 40

Please indicate why you chose the sample size proposed:

Sample size is convenient and selected based on available resources to demonstrate feasibility and the proof of concept effectiveness of EE therapy for COVID-19 patients admitted to ICU and post-ICU. We plan to recruit 40 eligible subjects.

G2. Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

P-values of 0.05 or less will be considered statistically significant based on a two-sided test unless otherwise noted. All variables will be tabulated descriptively at each scheduled time point (baseline and discharge date). For each continuous variable, the analyses will include the mean, standard deviation, minimum and maximum. For each categorical variable, the summary will include frequencies and percentages. Each variable will be analyzed using all available data. Baseline variables will be summarized using descriptive statistics. We assume that a successful intervention is also helpful to maintain subjects muscle mass, reduce neuromyopathy signs and increase venous return flow. The measured parameters (e.g. muscle circumference, sEMG, kent imaging, doppler, etc.) should change substantially from baseline to the end of the intervention. For example, the EMG amplitude values should show increased voltages. Next, for all continuous variables, pre-treatment scores will be regressed on post-treatment scores to form residualized change scores (e.g. sEMG, VPT, dynamometer, etc). Correlations will then be generated among these scores to determine whether changes in sEMG factors are related appropriately with increases in (clinically assessed) functional capacities and self-report measures of activities. ANOVA test will be used to examine significant difference between patients with severe risk factors for prolonged ICU stage (e.g. age, BMI, cardiovascular morbidities). Moderator effects will also be examined for exploratory purposes. Using gender as an example, mixed design ANOVAs will be conducted to determine whether mobility factors change over the course of treatment at different rates or with different patterns for men and women. Additional analyses will test whether changes in muscle strenght and neuropathy (e.g. VPT and dynamometer assessement at time of discharge).

Section H: Potential Risks/Discomforts

H1. Potential Risks/Discomforts

Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

The risk to participants of this study is considered to be minimal in a controlled environment with an attendant present. This research routine will not place subjects at higher risk than normal activities of daily living, and no more risk of harm or discomfort is associated with these tests than the discomfort normally incurred while performing normal muscle stretching. Subjects will be allowed rest time between trials as needed. The EMG device will detect level of fatigue and based on that we will determine the length of the sessions.

The devices and technology is completely non-invasive, safe, non-toxic and non-ionizing. The potential risks to subject are minimal. However, like any battery powered systems, there is a minimum risk of sensor malfunctioning. In addition, the study devices are not waterproof, and although they use a low powered battery (similar to a cellphone battery), in order to avoid any risk of shock the monitor should not be submerged or saturated with fluids during operations or cleaning. It does not emit any radiation to the human body, and does not offer any significant risk to the subject.

Subjects may experience mild discomfort from the sensor on their legs. We will inform the subject to please notify the investigators if the sensor is uncomfortable.

All information we will collect about the subject will be stored in a secure location and coded in a way to maintain confidentiality. Only study personnel will have access to their records. Data collected during the study may be published and made publicly available. Data may also be shared with other research groups. However, data that could in any way identify them will not be made public or shared.

Some of potential risks of using TENS therapy could be: * Skin related discomfort, such as tingling * Skin reaction to adhesive patch.

If the tingling sensation is too intense for the participant, they have the ability to reduce the intensity for their best level of comfort.

The risk to participants due to the optional assessments and surveys is considered minimal because all that is required is simple walking and balance movements in a controlled environment with an attendant present. This research routine will not place subjects at higher risk than normal activities of daily living, and no more risk of harm or discomfort is associated with these tests than the discomfort normally incurred while performing normal muscle stretching. Subjects will be allowed rest time between trials as needed.

Should the subject agree to the optional assessment involving the wearable sensor (PAMSys), the potential risks are considered minimal as well. This sensor will be used for assessing mobility performance and will perform physical tasks such as walking, sit-to-stand transitions, standing, physical activity monitoring etc. These assessments are non-invasive, safe, non-toxic, and non-ionizing as the other procedures described in this study. However, like any battery powered systems, there is a minimum risk of sensor malfunctioning. In addition, the study devices are not waterproof, and although they use a low powered battery (similar to a cellphone battery), in order to avoid any risk of shock the monitor should not be submerged or saturated with fluids during operations or cleaning. It does not emit any radiation to the human body, and does not offer any significant risk to the subject. The wearable sensors weigh less than .25 kg.

Potential risk to the subject due to the pulse oximeter optional test is considered minimal; this device is non-invasive, non-toxic, and non-ionizing. The device will be placed on the subject's finger, and monitor their oxygen levels.

H2. Data and safety monitoring plan

Do the study activities impart greater than minimal risk to subjects?

No

H3. Coordination of information among sites for multi-site research

Is the BCM Principal Investigator acting as the SPONSOR-INVESTIGATOR for this multi-site research?

No or Not Applicable

Is BCM the COORDINATING CENTER for this multi-site research?

No or Not Applicable

Section I: Potential Benefits

Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.

There is potential benefit of prevention or improvement of hospital acquired weakness due to prolonged hospital stay for participants, based on previous studies the electrical stimulation will improve blood flow, tissue perfusion and muscle

activation. The device is used to reduce pain. However, the proposed treatment may assist in preventing or improving hospital-acquired Weakness because of prolonged hospital stay . In addition, the participation in this study may help the investigators better understand how COVID19 may impact cause myopathy and neuropathy and how to best help these patients to recover from prolonged hospital-stay .

Primary outcomes include neuropathy (assessed using VPT test); muscle function (assessed using sEMG), and tissue oxygenation (assessed using Kent Imaging). Secondary outcomes include weakness (assessed using dynamometer); muscle atrophy (assessed by weight loss as well as measuring ankle, calf, and thigh circumference); venous return flow (Doppler US [optional]); frailty (frailtymeter [optiona]); hospital length of stay (patient medical record); and major adverse events (patient health record). The primary and secondary outcomes will be assessed at baseline (if feasible) and on biweekly basis up to 4 weeks or hospital discharge, whichever came first. Appropriate mixed models (linear for continuous or Generalized Estimating Equations (GEEs) for non-continuous or non-parametric variables) will be used to test the intervention effect for each of the primary (e.g., tissue perfusion, tissue oxygen delivery, neuropathy severity, and myopathy incident) or secondary (e.g., frailty, weight loss, MAE, etc) outcomes.

Also, participation may help the investigators design a practical assessing method to identify the impact of neuromyopathy in the hospital setting. This may allow physicians to provide personalized care by monitoring muscle loss and limb complications caused by prolonged hospital length of stay.

Describe potential benefit(s) to society of the planned work.

As described above, this type of work may allow physicians to provide more personalized care for hospitalized patients in need of physical therapy for continuous and prolonged periods, specially when having a severe illness that includes medical staff risk contact.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.

This study brings no more than minimal risk to subjects as it only involves a non-invasive device. There are some risks associated with lack of comfort from EE, skin allergy to the EE sticky patches that are used for delivering EE therapy, risk associated with electrical mal-function of EE, and other unknown risks. All EE devices will be checked before any use to minimize the risk associated with electrical malfunction. All EE devices are FDA approved for the purpose of pain reduction. However, these devices have not been used before for purpose of managing COVID-19 side effects like the purpose of this study.Although there is no direct benefit for participating in the study, their participation may help the investigators design a practical assessing method to identify the impact of Neuromyopathy in the hospital(inpatient) setting.

Section J: Consent Procedures

J1. Waiver of Consent

Will any portion of this research require a waiver of consent and authorization?

No

J1a. Waiver of requirement for written documentation of Consent

Will this research require a waiver of the requirement for written documentation of informed consent?

No

J2. Consent Procedures

Who will recruit subjects for this study?

PI
PI's staff

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.

Phase I: Subjects will be recruited from the hospital. They may get some referrals from other collaborators. In order to recruit or identify subjects, we will screen our patient charts for eligible subjects. The COI will identify eligible subjects and alert the coordinator. The coordinator will review all the details of the study with the subject and/or their family. If the subject agrees to participate in the study, they will be screened and then enrolled into the study.

We will be conducting the study during the first 48 hrs of hospitalization due to COVID-19, in case the patient is not capable to consent we will ask for consent from their legal authorized representative. The legal representative will be consented the same way the patient would but over the phone by stating the procedures/ benefits/ risks and ask questions. When the patient regain consciousness, he/she will be fully informed about the study, and will verbalize

understanding and voluntarily agree to participate with the guidelines as stipulated in the informed consent.

The discussion will be documented in the subject's medical record or research chart. Two copies of the unsigned consent form will be sent to the subject/legal representative with instructions for completion of the signature page and assent (if applicable). Signatures will be obtained according to standard Baylor IRB regulations. The subject will be told to keep one form and returned the other to the investigator by mail, email, or fax. The Baylor Investigator/designee will sign the consent form when returned from the subject. The signed consent form will be maintained in research records.

The subject will be informed if he/she can withdraw from the study at any time without loss of benefits. Consent forms will be signed and dated by the subject and by the Principal Investigator or Investigators. The original (with patient's signature) will be maintained per IRB policy. Any critical information will be sent for inclusion in the medical records, if it affects patient's well-being and any future treatment. A signed copy of the consent form will be provided to the patient. Informed consent will be obtained prior to performance of any study procedures. Specifically: 1. No minors will be consented. 2. Subjects are given as much time as needed to ask questions and read over the consent. They are will be given a copy of the consent and can return at a later date if they need to discuss it with family members, etc. There will be an attachment in section S for the waiver of consent the form was retrieved from Section J- Adult assent.

Phase II: Subjects will be recruited from the COVID-19 clinic after their first visit. They also may get referral from other collaborators. To recruit or identify subjects, we will screen our patient charts for eligible subjects. The COI will identify eligible subjects and alert the coordinator who will screen the subject and review study details with the subject and/or their family. If the subject agrees to participate in the study, they will be enrolled into the study.

Patients enrolled will be alert and aware, there will not be patients with loss of consciousness enrolled in this phase. Optional assessments or surveys are not primary outcomes and so this information will not be collected from previously enrolled subjects. PI/research staff will review the study and ICF with subject, asking questions to gauge comprehension. Control group subjects who already completed the study will be called to assess willingness to participate for 4 more weeks with an active device. If they agree, they will be reconsented in-person at the next visit or an email copy will be sent to sign and return via email. Completed active group subjects will be called and reconsented. The consent form will be sent via email and we will request that they email the signed copy back. Signed ICF will be kept in research records and a copy will be sent to all subjects via email.

Are foreign language consent forms required for this protocol?

No

J3. Privacy and Intrusiveness

Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?

No

J4. Children

Will children be enrolled in the research?

No

J5. Neonates

Will non-viable neonates or neonates of uncertain viability be involved in research?

No

J6. Consent Capacity - Adults who lack capacity

Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?

Yes

J7. Prisoners

Will Prisoners be enrolled in the research?

No

Section K: Research Related Health Information and Confidentiality

Will research data include identifiable subject information?

Yes

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.

Yes

Specific information concerning alcohol abuse:

Yes

Specific information concerning drug abuse:
Yes

Specific information concerning sickle cell anemia:
No

Specific information concerning HIV:
No

Specific information concerning psychiatry notes:
No

Demographic information (name, D.O.B., age, gender, race, etc.):
Yes

Full Social Security #:
No

Partial Social Security # (Last four digits):
No

Billing or financial records:
Yes

Photographs, videotapes, and/or audiotapes of you:
Yes

Identifiable biospecimens
No

Other:
No

At what institution will the physical research data be kept?
The physical research will be kept in our BCM offices housed in the Mcnair Building room B10.401.

How will such physical research data be secured?
Data will be kept in locked file cabinets that only the research team has access to.

At what institution will the electronic research data be kept?
Data will be kept locked on network computers in our BCM offices, under the password protected server.

Address:\\discovery1.ad.bcm.edu\bcm-dept-icamp

Additional electronic data may be stored on REDCap. REDCap is hosted by Baylor College of Medicine - Institute for Clinical & Translational Research.

Such electronic research data will be secured via BCM IT Services- provided secured network storage of electronic research data (Non-Portable devices only):
Yes

Such electronic research data will be secured via Other:
Yes, (describe below):
Electronic data will be stored using the REDCap (Research Electronic Data Capture) software. This software is used to electronically collect and manage research data. REDCap is a secure, web-based platform.

Electronic data will also be stored and secured under the password protected server provided by BCM IT Services.

Will there be anyone besides the PI, the study staff, the IRB and the sponsor, who will have access to identifiable research data?
Yes, identify the classes of the persons:
People who ensure quality from the institutions where the research is being done, federal and other regulatory agencies will have access to all of the research data.

Please describe the methods of transmission of any research data (including PHI, sensitive, and non-sensitive data) to sponsors and/or collaborators.
Transmissions, if any, will only happen via secure emails.

Will you obtain a Certificate of Confidentiality for this study?

No

Please further discuss any potential confidentiality issues related to this study.

NA

Section L: Cost/Payment

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.

All clinical/standard procedures will be billed to the subject's insurance. These include, physician visits, debridement, medications prescribed by physician.

There will be no research procedures charged to the subject or their insurance. This includes, the research device, materials provided by the research team, visits with the research team.

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.

Dollar Amount:

350

Distribution Plan:

For taking part in this research, the subject may be paid up to a total of $350. Their compensation will be broken down as follows:

Subjects will be paid $50 for every visit completed visit. There are a total of up to 7 visits. Payments will be done using the ClinCard method. Their SSN will be requested for the research team to issue the payments. The research study will also cover the subject's parking or transportation expenses to go to their research visits.

Section M: Genetics

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.

Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family member's confidentiality?

Section N: Sample Collection

None

Section O: Drug Studies

Does the research involve the use of ANY drug* or biologic? (*A drug is defined as any substance that is used to elicit a pharmacologic or physiologic response whether it is for treatment or diagnostic purposes)

No

Does the research involve the use of ANY gene transfer agent for human gene transfer research?

No

O1. Current Drugs

Is this study placebo-controlled?
No

Will the research involve a radioactive drug?
No

Section P: Device Studies

Does this research study involve the use of ANY device?
Yes

Device 1: Trigno Wireless EMG System

Device 2: Tennat Biomodulator

Device 3: Legsys

Device 4: Frailty Meter

Device 5: Balansens

Device 6: Pamsys

Device 7: Pulse Oximeter

Section Q: Consent Form(s)

Effectiveness of lower extremity electrical stimulation therapy in patients with COVID-19 (Phase I)

Effectiveness of lower extremity electrical stimulation therapy in patients with COVID-19 (Phase II)

Section R: Advertisements

None