Effects of an Electrical Stimulation Program on Strength, Functional Capacity, Pain, and Gait in Individuals With Knee Osteoarthritis

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Introduction

Knee osteoarthritis (KOA) is a degenerative joint disease that affects the knee and loss of cartilage[1], resulting in pain; quadriceps weakness; and swelling, locking, and giving way of the knee[2]. The severity of KOA based on radiologic findings can be graded using the Kellgren & Lawrence (K&L) scale, a measure that ranges from 0 to 4, with 0 being none and 4 being severe[3]. Depending on the severity of the disease, symptoms of KOA may be managed by non-surgical or surgical interventions, such that non-surgical management is recommended to delay the need for invasive joint replacement procedures[4], and surgical treatment is most beneficial for those at the severe stage who have exhausted conservative measures[2]. Despite these means, the extent of patients with KOA who engage in interventions to delay disease progression and operative procedures is low.

Conservative treatment of KOA includes exercise[4] to alleviate pain, improve strength[5], and improve quality of life and physical function[6]. However, exercise interventions involve a physical capacity that may be challenging for the KOA community[7]. In fact, adults with radiographic KOA spend an average of 67% of their daily waking hours in sedentary behavior[8]. This proportion of sedentary time may lead to disuse atrophy, or atrophy of muscle fibers due to prolonged unloading[9], which may reduce muscle mass and strength, impair mobility, and hasten the need for surgery[10]. Additionally, physical inactivity may have a detrimental effect on quality of life for persons with KOA[11], further contributing to the disease burden[12]. Given the limited options to maintain muscle mass or strength if patients with KOA are unwilling or unable to exercise, alternative therapies, such as electrotherapy, have been proposed.

Electrotherapy, or electrical stimulation delivered to target muscles using an external stimulator connected to electrodes and surface hydrogel pads, has been widely used for treatment, rehabilitation, and training purposes. Electrotherapy interventions, such as neuromuscular electrical stimulation (NMES) and functional electrical stimulation (FES), have resulted in improvements in gait performance[13,14] and increased quadriceps strength[15,16] to counteract muscle decline. This is reasonable as NMES produces muscular contractions[38], and FES provides stimulation with a targeted movement, such as walking, to mimic normal voluntary kinematics[39]. On the contrary, there are studies that do not support NMES for pain management[17] and objective measures of function[18]. However, those studies explored the application of NMES alone and excluded studies combining electrical stimulation interventions with exercise. Additionally, there are limited studies exploring FES in the KOA population despite its positive effects in walking speed[40, 41], lower limb kinematics[41], and muscle mass and strength[42] in the stroke and multiple sclerosis communities. Pairing electrical stimulation with exercise has been employed to improve muscle activation in the affected leg of hemiplegic patients[19] and provide a greater stimulus for muscle hypertrophy than stimulation or exercise alone when voluntary activation deficit is present[20], thereby confirming the value of combined electrotherapy for those with impaired limbs. This combined intervention was also supported as an effective alternative to relieve pain, increase quadriceps strength, improve physical function and functional performance in patients with KOA who have difficulty performing an exercise program[21]. Although there are inconsistencies regarding electrotherapy for the KOA community, there should be a recognition

and utilization of electrotherapy combined with activities to promote physical activity and better manage some symptoms associated with the disease.

Acknowledging the benefits of combined electrotherapy and KOA as a progressive and degenerative condition with unlikely regression or restoration of damaged structures, the study aims to investigate the effects of stimulation assisted activities to delay the disease progression and muscle atrophy in those with KOA. Thus, the purpose of this research is to investigate if stimulation assisted (NMES and FES) activities can combat disuse atrophy for individuals diagnosed with KOA. This study will use a home-based medical device (Cionic Neural Sleeve NS-100, K213622, CIONIC, San Francisco, CA) to administer electrical stimulation and measure its effect on outcomes that include quadriceps strength, perceived functional capacity, pain, and walking performance.

Significance

Adults with KOA spend most of their day engaging in sedentary behavior and report worse physical function[8], which may lead to progression of the condition, increased functional dependence and decreased quality of life[22]. Existing literature shows that NMES assisted exercise may counter disuse atrophy in sedentary individuals[23], but because there has been minimal research investigating the effects of FES in the KOA community, exploration of this study is warranted.

Figure 1: Cionic Neural Sleeve system

Note: Left: Cionic Neural Sleeve showing the configuration of the FES and electromyographic (EMG) electrode arrays. Center: Cionic mobile application interface for setting FES parameters (frequency, pulse width, intensity) and current field steering. Right: Cionic Neural Sleeve on body.

Research Objectives

1. Analyze the effects of electrical stimulation assisted interventions versus a conventional exercise program on muscle strength, perceived function, and pain in KOA.
2. Compare the effects of unassisted walking and stimulation assisted walking on walking performance in KOA.
3. Measure the compliance of electrical stimulation assisted interventions to a conventional exercise program on the effects of pain and perceived function in KOA.

Hypotheses

It was hypothesized that combined electrotherapy groups will show larger muscle mass and strength improvements; improved gait kinematics, pain and perceived function; and a high compliance to the assigned program compared to the unstimulated group.

Specific Aims

This protocol describes a study intended to evaluate the Cionic Neural Sleeve for subjects diagnosed with KOA. CIONIC will use this study as an opportunity to validate FES for disuse atrophy in KOA. CIONIC will use lab visits (Table 1) to record participants' strength, kinematic gait metrics, walking performance, self-reported functional capacity and pain.

The Cionic Neural Sleeve has been evaluated for safe use in a simulated at-home environment under prior studies (CIONIC-02-001 and CIONIC-03-001).

There are two specific aims with this study:

Aim 1 – Validate FES for disuse atrophy in KOA

The study intends to obtain evidence to support the use of the FES for disuse atrophy in the KOA community. Standard clinical assessments will be collected at meaningful endpoints in the study to allow CIONIC to measure subjects' performance over time.

Aim 2 - Provide statistically significant evidence

The study design is a randomized controlled trial, where CIONIC will collect spatial and kinematic metrics to track participants' mobility and gait patterns. Some examples of these metrics may include: gait speed, total steps, step variability, and foot-floor angle at heel strike.

Table 1: Schedule of events

Initial visit	● Verify consent ● Gather demographic information and anthropometric measurements ● Measure strength, walking performance, thigh muscle volume, functional ability of the lower limb ● Distribute questionnaires on perceived functional capacity, pain, and quality of life ● Prescribe exercise and walking program ● Random assignment of groups ● Distribute the Cionic Neural Sleeve and provide Instructions for Use
6 week study midpoint	● Measure strength, walking performance, thigh muscle volume, functional ability of the lower limb ● Distribute questionnaires on perceived functional capacity, pain, and quality of life
End of study	● Measure strength, walking performance, thigh muscle volume, functional ability of the lower limb ● Distribute questionnaires on perceived functional capacity, pain, and quality of life ● Collect equipment

Participation Selection and Randomization

A sample size of 32 participants was calculated to be sufficient for a two-tailed significance level of 5% and a power of 80% (Appendix A). This was adjusted to 45 participants with knee osteoarthritis to allow for dropouts. Recruitment for this study will be conducted using a recruitment flyer and through the CIONIC website. Recruitment will be based on a first come

basis. Interested participants will complete a questionnaire to be reviewed according to the inclusion and exclusion criteria. Responses will then be reviewed, and prospective participants will be invited to schedule a virtual meeting with a study staff member who will screen the prospective subject for an understanding of the study and for their voluntary participation. All participants will be assigned a unique number using a computer random number generator and randomly assigned to a group by a researcher. All participants will receive their assigned intervention at their first lab visit.

Inclusion Criteria

- Persons with knee osteoarthritis between the ages of 22 and 75
- Ability to walk a duration of 30 minutes per walking session (with or without an assistive device), for three days per week
- Able to tolerate the device for up to 1 hour per lab session
- No recent change in medication or exacerbation of symptoms over the last 60 days
- Radiographic KOA K&L grade 2 or 3 or physician diagnosed mild or moderate KOA if radiographic imaging is not available
- No hyaluronic acid or cortisone injection into knees in previous 12 months

Exclusion Criteria

- Lower motor neuron disease or injury (e.g. peripheral neuropathy) that may impair response to stimulation
- Absent sensation in the impacted or more impacted leg

- Inadequate response to stimulation, as defined as inability to achieve muscle contraction or tolerate stimulation
- Inability to ambulate with the sleeve in place of an ankle foot orthosis (AFO)/knee ankle foot orthosis (KAFO) if utilized
- Use of FES devices in the past year
- Demand-type cardiac pacemaker or defibrillator
- Malignant tumor in the impacted or more impacted leg
- Existing thrombosis in the impacted or more impacted leg
- Fracture or dislocation in the impacted or more impacted leg that could be adversely affected by motion from stimulation
- History of knee surgery
- History of other types of arthritis
- History of neurological disease
- History of seizures or diagnosed with epilepsy/seizures
- Current pregnancy

Methodology

Overview of Study

This study is a randomized controlled trial. Figure 2 depicts a flow diagram of the study design. Participants will be screened for eligibility through a questionnaire, and after study details are explained and consent is obtained, they will be invited to the study site. Assessments will be conducted at CIONIC Inc., and involve approximately 45 patients for a 12 week study period.

All subjects will be assigned an electrical stimulation system to wear on the most impacted leg and be prescribed a home-based exercise and walking program. Subjects will be randomly assigned into three groups: (a) control; (b) NMES+; (c) NMES+FES. The control group will not receive stimulation for the exercise and walking program, whereas subjects in NMES+ will receive stimulation during exercises, and subjects in the NMES+FES group will receive stimulation during exercises and walking. Outcome measures will be assessed at baseline, 6 weeks after baseline, and end of study (Table 2). Equipment and additional feedback will be collected at the end of study. These three groups will be analyzed using several outcome measures. Primary outcome measures of the study are quadriceps strength, perceived functional capacity, self-reported pain, and walking performance. Secondary interest will be adherence to program, thigh muscle volume, functional ability of the lower limb, and quality of life. The CIONIC system will be used to track adherence (duration of sessions, frequency of use).

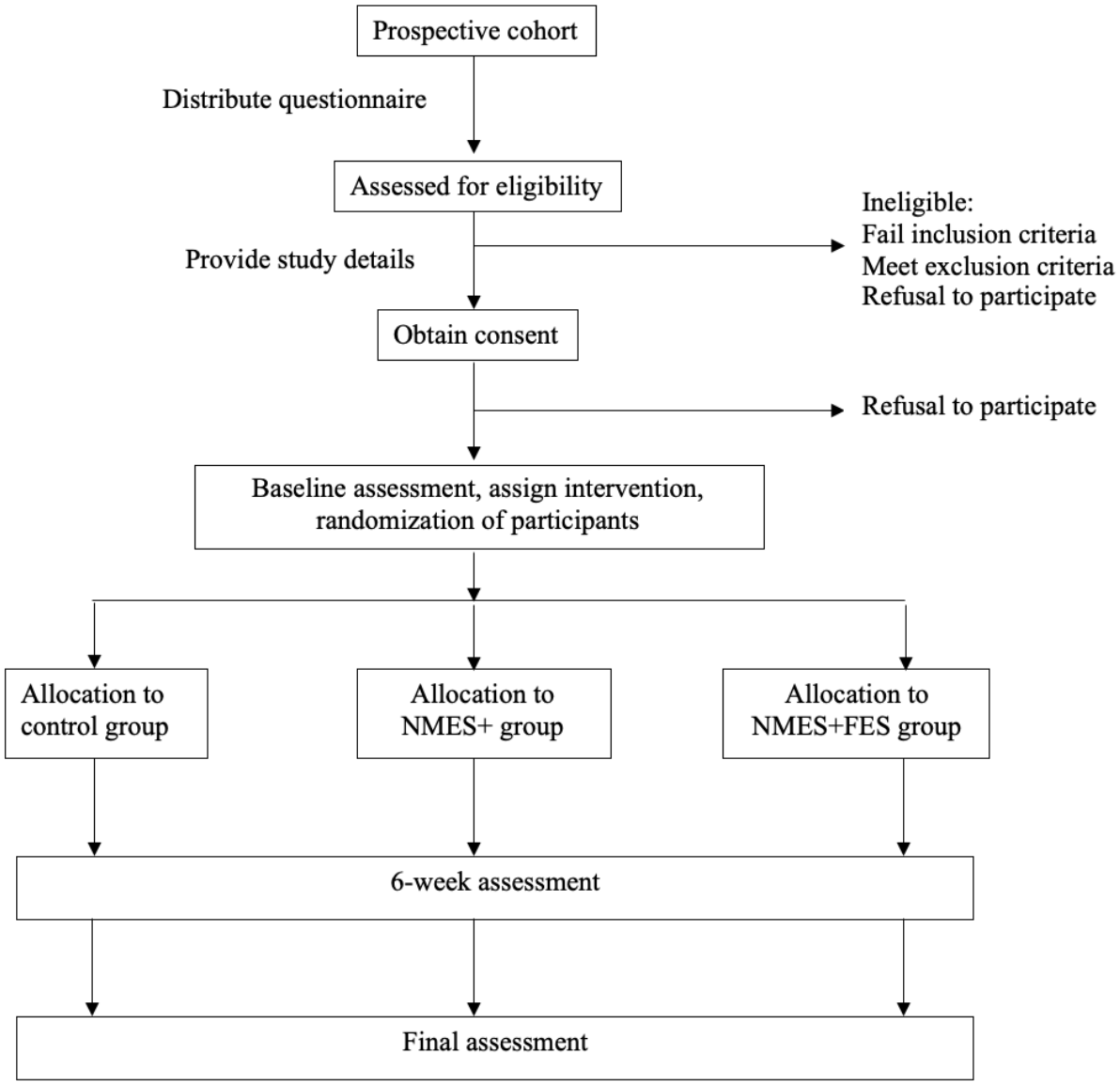

Figure 2: Study flow

Table 2: Study overview

Comparison Groups	Treatment Schedule	Timing and Outcome Measures
Control (unstimulated exercise and walking) NMES+ (NMES+exercise and unstimulated walking) NMES+FES (NMES+exercise and FES+walking)	Exercise: 5x/week for 12 weeks Progression every 3 weeks Walking: 10 min, 3x/week for 12 weeks Progression up to 30 min by end of study	At baseline, midpoint and end of study: Quadriceps strength Perceived functional capacity Self-reported pain Walking performance Thigh muscle volume Functional ability of lower limb Quality of life EMG activity Weekly: Adherence to program

Participant Identification, Recruitment & Informed Consent

CIONIC researchers will follow a recruitment plan (Figure 3). CIONIC will post a recruitment flyer on their website and interested participants may send an email directly to trials@cionic.com. CIONIC may also recruit directly from physical therapy providers and osteoarthritis advocacy groups through a recruitment flyer with their permission. The study staff will email interested candidates a screening questionnaire to assess for study eligibility. CIONIC researchers will then contact qualified candidates to set up a Zoom meeting to explain study details, address risks and benefits, and answer questions. Those who opt to participate in the study will receive an electronic consent form via DocuSign for their review and electronic signature. A member of the CIONIC team will guide the participant through the informed consent document, and answer concerns. Participants who sign the informed consent document will receive a copy for their records and proceed with the study. All forms will be stored on a secure server. After consent is obtained, the CIONIC researchers will schedule the subject to report to the study site for initial assessment.

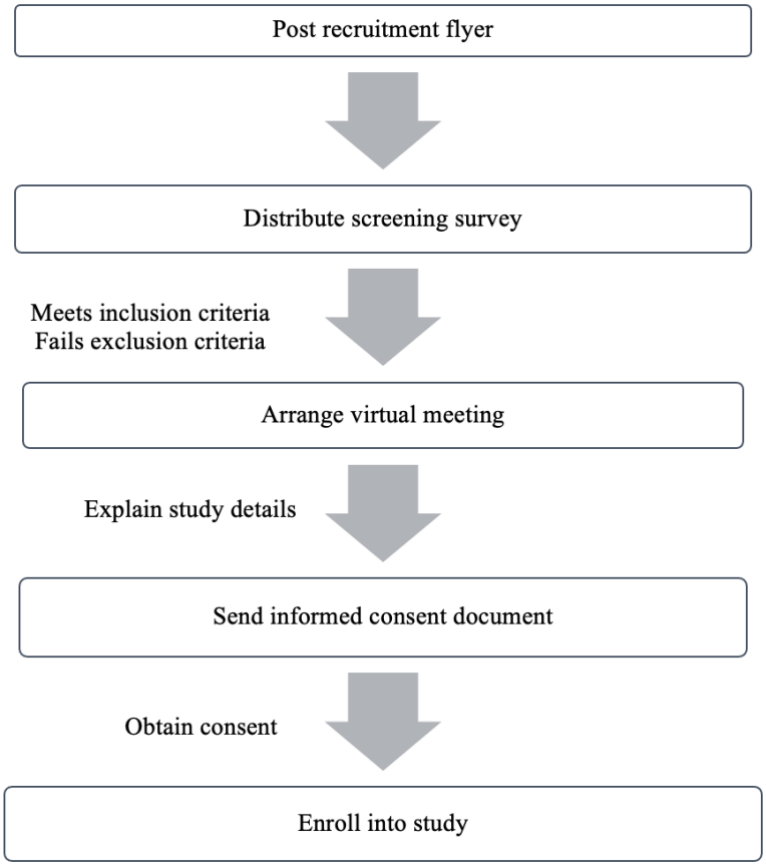

Figure 3: Recruitment plan

Participant Capacity and Comprehension

The study's inclusion criteria and recruitment plan may include individuals with decision making impairments and/or language and communication impairments. To mitigate this, the video conference call will further screen and determine if the severity of their impairments will require additional safeguards or if the interested party will need to be excluded from the study.

Lab Visits

The study will be explained to the participants and written informed consent will be obtained before the initial lab visit. Physical measurements, performance tests, and questionnaire responses will be collected at three lab visits: initial, study midpoint (6 weeks), and end of study (12 weeks). Physical measurements will include height, weight, and thigh circumference of the impacted leg. If subjects report bilateral compromised legs, the most impacted/painful leg will be measured. Participants will be asked to complete four performance tests (maximal voluntary isometric contraction of the quadriceps, Five Times Sit to Stand Test (FTSST), 10-meter Walk Test (10mWT), and the 6-Minute Walk Test (6MWT)) and three questionnaires (Western Ontario/McMaster Universities Osteoarthritis Index physical function (WOMAC-PF) subscale, WOMAC-pain, and the Short Form-36). Order of the tasks at the lab visits are as follows: maximal voluntary isometric contraction of the quadriceps, FTSST, 10mWT, WOMAC-PF, 10mWT, WOMAC-pain, 6MWT, Short Form-36, and 6MWT. Instruction will be provided to the participants before beginning a new task, and the researchers will periodically gauge the subjects for a need for a break and understanding of the task. For the walking tests, subjects will be fitted with the electrical stimulation system to collect EMG/kinematic data, and depending on the subject's group assignment, stimulation may or may not be enabled. All subjects will be provided with and instructed to wear the electrical stimulation system for the subsequent 12 weeks. All subjects will be taught how to navigate the supporting app and receive a user manual on how to operate/care for the system. Subjects assigned to receive stimulation will be taught how to adjust parameters of the device using the supporting app. All participants will receive a handout explaining the exercise, and a calendar for the exercise and walking program (Appendix

B). Subjects will be informed to perform the exercise and walking program in an area free from obstacles. Lab visits may be up to 90 minutes in duration.

Exercise and Walking Program

The participants will wear the device during the 12-week exercise and walking program. This may range from 1 minute to 35 minutes per day (Appendix B).

Exercise Program

All participants will be prescribed the same exercise program and instructed to adhere to the program for 5 days per week for 12 weeks, for a total of 60 exercise sessions. This program requires isometric quadriceps contractions in a supine position with a rolled-up towel placed behind the knee. For this study, subjects will contract their thigh muscle to straighten their knee for three seconds and relax for three seconds for a repetition, as prompted by the supporting app. Participants in this study will be instructed to perform sets of 10 repetitions, with a progression every 3 weeks (Table 3). For exercise sessions requiring more than 1 set, the sets should be separated by 30-second rest intervals.

Table 3: Exercise Program

Exercise	Frequency	Progression
Isometric quadriceps contraction	5 days per week	Weeks 1-3: 1 set of 10 Weeks 4-6: 2 sets of 10 Weeks 7-9: 3 sets of 10 Weeks 10-12: 2 sets of 10, twice per day

Walking Program

All participants will be prescribed the same walking program, where subjects will be instructed to walk 3 days per week for 12 weeks, for a total of 36 walking sessions. At the start of the study, participants will walk for 10 minutes and then gradually increase walking time up to 30 minutes per walking session by the end of the study.

Electrical Stimulation System

Electrical stimulation will be given using the Cionic Neural Sleeve, a wearable single channel stimulator with a monophasic rectangular pulse. The Cionic Neural Sleeve system consists of a Nylon/Lycra garment equipped with small metal electrodes covered by reusable 1.75” x 1.75” electrode pads that adhere to the skin’s surface and a Control Unit. Small wires are routed through the interior of the sleeve from each metal electrode and electrode pad to a handheld removable Control Unit that houses the central computing module and battery. There are flaps on the upper and lower leg that are secured in place with Velcro, and an upper thigh pocket to hold the Control Unit. The Control Unit connects to the sleeve via a short connector located in the upper thigh pocket and communicates with a smartphone via the CIONIC application using Bluetooth™ Low Energy (BLE). The device is a Food and Drug Administration (FDA)-cleared Class 2 medical device.

Study Removal and Device Returns

If participants have questions during the study, they may call, text (cell phone number 925-788-6649), or email the primary investigator (PI) directly (rebecca@cionic.com) at any time. If a participant loses or damages the system (Control Unit or the Cionic Neural Sleeve), the equipment will be replaced via next day freight or by in-person pickup from the lab site. Broken or damaged equipment may be returned to the lab in person or CIONIC will mail a return shipping label and box. Under no circumstances will the participant be financially responsible for any damaged devices or associated shipping costs. If a participant chooses to withdraw from the study, they may return the equipment to the lab in person or CIONIC will mail them a return shipping label and box. Participants who lose or irreparably damage two sleeves or Control Units may be asked to withdraw from the study early but will be compensated for their time.

Primary Outcome Measures

Quadriceps Strength

Quadriceps strength, as measured by maximal voluntary isometric contraction (N), will be assessed using a handheld dynamometer according to a testing protocol[24] for both limbs. To assess maximal voluntary isometric contraction of the quadriceps, participants will be seated with the back erect and legs hanging over the edge of the treatment table. The researchers will visually ensure that the subjects are sitting upright before administering the test, but if the subjects are not seated upright, the researchers may give them a tactile cue for posture if needed. With the handheld dynamometer placed distally on the affected leg with the knee in 90 degrees flexion, participants will push against the dynamometer for 5 seconds. Subjects will get two

warm-up trials separated by a 1-minute rest period. The first warm up will be at 50% maximal effort, and second trial at 70% maximal effort, with contractions to be held for 5 seconds. Subjects will then perform 3 repetitions of maximal effort, separated by two minutes of rest between each. The test will be repeated on the other leg. The average of the 3 repetitions will be recorded as the subjects' 1 repetition maximum, the gold standard for evaluating dynamic strength in non-laboratory conditions[25].

Perceived Functional Capacity

The WOMAC-PF is a 17-item questionnaire that measures the impact of KOA on daily physical activities in the past 48 hours[26]. Scores on the WOMAC-PF range from 0 to 68, with high scores indicative of worse functional limitations[26]. The minimal clinically important difference (MCID) for improvement of 14.48[27] will be used as a benchmark.

Pain

The WOMAC-Pain is a 5-item survey that prompts the respondent to reflect on the quality of pain in 5 activities during the last 48 hours[26]. Scores range from 0 to 20, with high scores indicative of worse pain[26], and the MCID of 8.74[27] will be used as an indicator of improvement in our study.

Walking Performance

Walking performance will be evaluated by gait speed and walking endurance. All subjects will wear the Cionic Neural Sleeve during the walking tests, and all subjects will perform the same number of tests. The control group will perform the walking tests in unstimulated conditions. Unstimulated conditions require subjects to wear the Cionic Neural Sleeve as they traverse to collect EMG/kinematic data, but stimulation will not be enabled. Subjects assigned to receive the stimulation intervention will perform the walking tests in unstimulated conditions before traversing in stimulated conditions. Stimulated conditions require subjects to wear the Cionic Neural Sleeve and receive stimulation assistance while walking.

Gait speed (m/s) will be measured using the 10mWT on a 10-meter walkway with brightly colored tape to indicate boundaries, two chairs, a stopwatch/timer, and the subject's usual walking aid. During this performance test, the subject will walk with the Cionic Neural Sleeve for 10 meters, and time will be measured for the intermediate 6 meters. Two trials will be administered at the subject's comfortable walking speed, followed by two trials at fast walking speed. Rests will be provided between each trial. The trials for each speed and stimulation condition will be averaged. Acceleration and deceleration will occur outside of the timed portion to allow for a more accurate assessment[28]. Prior literature reported an improvement of 0.12 m/s in patients with unilateral KOA post-surgery[29,30], and this will be used as a point of comparison in our study.

Walking endurance (m) will be measured using the 6MWT using the same walkway utilized for the 10mWT. Participants will wear the Cionic Neural Sleeve during the two 6MWTs. For the 6MWT, the subject will be instructed to walk as far as possible for 6 minutes, up and down the pathway, and pivoting to turn at the end of each lap[31]. Timing will begin when the participant steps over the start line, and distance traveled will be recorded. Encouragement outlined in the guideline (Appendix C) will be given to the subjects after each minute, and participants will be instructed to stop at 6 minutes or prior, if they are unable to complete 6 minutes. Use of a walking aid and standing rests will be permitted. Normative values of people aged 40-80 years will be used as reference values[32].

Secondary Measures

Adherence to Program

Adherence to the program will be measured by the usage log of the Cionic Neural Sleeve. The data collected from the Cionic Neural Sleeve worn on the affected limb/most affected limb will be recorded to monitor compliance to the program in number of repetitions and duration of walking.

Thigh Muscle Volume

Thigh muscle volume will be estimated using a measurement tape for thigh circumference and a prediction model. Thigh circumference (cm) will be measured from a point 15 cm proximal to the superior pole of the patella. The prediction model is as follows: Muscle volume (cm^3)

=4226.3 − 42.5×age(year) − 955.7× gender(male=1, female=2) + 45.9×body weight(kg) + 60.0×thigh circumference(cm)[33]. It was selected for this study for its correlation ($r^2 = 0.745$) to magnetic resonance imaging, the gold standard of measuring muscle volume[37].

Functional Ability of the Lower Limb

To measure functional ability of the lower limb, subjects will be asked to perform the FTSST. The FTSST requires participants to sit in a chair with their arms crossed over the chest and then to stand up/sit down for five times, as fast as possible[34]. Subjects will be timed from the initial sitting position to the final standing position. Cut-off points of 10.8 and 12.8 seconds will be used as references for intermediate and poor function, respectively[35].

Quality of Life

The Short Form 36 (SF-36) is a generic measure of health status that measures self-reported functional health and well-being in the past four weeks in eight domains or two summary scores. Scores range from 0 to 100, with 0 representing extreme interference, and 100 representing no interference[36].

Other information to be collected include date of birth, gender, ethnicity, height, weight, duration of condition, and type and dosage of medication.

Data Analysis/Statistical Analysis

For each of the primary and secondary measures, we will perform a Shapiro-Wilk test for normality to assess the assumption of normality. If the outcome variable is approximately normally distributed, a paired t-test will be used to statistically compare outcome metrics before and after the intervention within a condition. If the normality assumption is not met, the Wilcoxon signed rank test will be used as an alternative to the paired t-test for this statistical comparison. Bonferroni multiple hypothesis correction will be utilized for a corrected significance level.

To compare across conditions, an analysis of variance (ANOVA) test will be performed if the outcome variable is normally distributed. If the normality assumption is not met, the Kruskal Wallis test will be used as the non-parametric version of ANOVA. We may also employ a repeated measures ANOVA test for inclusion of all three timepoints.

Organizational Relationships

CIONIC works closely with Edge Analytics, a consulting firm who has been contracting for CIONIC for over two years. The firm is primarily responsible for algorithm development and statistical analyses of kinematic and EMG data. Ren Gibbons, Lauren Goodman, PhD, and Brinnae Bent, PhD are employees of Edge Analytics who have been working closely with Cionic. Brinnae Bent is a sub-investigator on this study.

Risk & Benefit Assessment

The Cionic Neural Sleeve has been tested extensively in previous studies. Across these prior studies, the Cionic Neural Sleeve has been evaluated for walking and exercise mode, approved for FDA 510k submission and its intended use in a simulated home environment, and for home usability with no adverse events.

However, any study of this kind comes with some known risks, that although rare, are associated with participation:

- Discomfort from the electrical stimulation
- Minor skin irritation at the sites of sensor/electrode pad placement
- Muscle fatigue from prolonged device use
- Anxiousness due to the anticipation of receiving an electrical stimulation
- Injury caused by unintended falls while using the Cionic Neural Sleeve
- Exposure to coronavirus disease 2019 (COVID-19) or other communicable disease

It is not always possible to know all the risks associated with a study such as this one. If any new risks are reported for this study, a member of the study team will inform the participant so that they can decide whether they would like to continue in the study.

Risk Mitigation Strategies

CIONIC has taken the following actions to reduce the risks to participants:

1. Evaluated the Cionic Neural Sleeve across 42 mobility-impacted adult participants for formative and summative Human Factors testing required for FDA 510k submission (CIONIC-02).
2. Extensively tested (more than 2 hours) the Cionic Neural Sleeve during walking and exercise mode on 32 mobility-impacted candidates in a lab setting (CIONIC-01) and on 17 subjects in their home environment (CIONIC-03) with no adverse events.
3. Modified system design to improve usability and increase safety.
4. Comprehension of the study tasks will be discussed with the participant prior, and their comfort will be monitored throughout the study.
5. A clinician (PT) is included in the study team and will be present at the initial visit, as well as advising for the home use instructions.
6. The testing area will be safe, well-lit and clear of all obstacles.
7. The CIONIC team is trained to strictly follow the study protocols.
8. Participants are provided with access to the Cionic Neural Sleeve Instructions for Use.
9. Participants are provided with instructional videos within the CIONIC app.
10. Participants will be provided CIONIC's contact information to answer questions and provide technical support throughout the study.
11. Participants will manage their walking speed and control the electrical stimulation intensity at their own comfort.
12. The research team will wear masks upon request by the participant to minimize exposure to communicable diseases.

13. The research team will instruct subjects to wear the Cionic Neural Sleeve in an area of their home environment that is free from obstacles.
14. A Use/Application Hazard Analysis was performed during the development of the Cionic Neural Sleeve, and risks related to stimulation were considered and evaluated. Use-related errors related to these risks were validated in human factors study.

Benefits

Participants in this study will be early adopters of the Cionic Neural Sleeve system and may benefit from the product in a few distinct ways:

1. Performing routine exercise (with or without stimulated assistance) has been shown to improve general health, strength, and pain.
2. Walking with a stimulation device may facilitate neural retraining which could result in improved motor control, pain, and walking performance. Although this has been anecdotally reported in previous studies, CIONIC hopes to establish this with clinical endpoints in this study.
3. If requested, CIONIC will provide the participant with a copy of their data, which the participant may choose to share with members of their clinical team to support their care. CIONIC is not a medically licensed company and cannot and will not provide medical advice; however, CIONIC will explain the data in more detail to the participant if requested.

Study Withdrawal

During the consent process, participants will be informed that they may withdraw from the study at any time. The study team member responsible for reviewing informed consent will confirm that they understand that they have this option. Participants will be entitled to financial compensation for each lab visit. The investigators or sponsors may stop the study or take participants out of the study at any time should they judge that it is in their best interest, if subjects experience a study-related injury, if subjects need additional or different medication/treatment, or if they do not comply with the study plan. The researchers may remove participants from the study for various administrative and medical reasons. Participants will not be compensated for lab visits that they cancel or miss.

Data Storage, Monitoring and HIPAA

This study involves the collection of data from sensors on the Cionic Neural Sleeve system, and possibly external kinematic data collection systems for validation. Data collected will not include personally identifiable information. The devices comprising the system connect wirelessly via BLE to an application running on a smartphone or iPad.

CIONIC's smartphone or iPad's camera will also record video of the lower body at the lab visits. The participant's face and voice will not be recorded. The content of the data will be uploaded to a secure server. Each set of data will be organized using a unique numerical identifier that does not include protected health information (PHI) (e.g., initials) will be stored in our Health Insurance Portability and Accountability Act (HIPAA) compliant database with access limited to

CIONIC employees who will administer the study. This unique identifier (date of testing and study session) will be recorded separately in a participant tracking file which will include demographic data such as gender, age, diagnosis, and duration of diagnosis. Adverse events (AEs) and protocol deviations will be recorded for each participant. This data will also be stored on a secure server.

The PI, Rebecca Webster, will be responsible for ensuring participants' safety on a daily basis. Data collected from this study will be reviewed on a weekly basis by the PI and sponsor for each week there are study participants. All data will be collected and stored on a secure server. There is no Data and Safety Monitoring Board for this study.

All AEs will be reviewed by the PI within one business day of occurrence. AEs determined to be Serious adverse events related to subject safety will be reported to Salus Institutional Review Board within one business day of review by the PI. AEs and unanticipated problems will be reviewed on a monthly basis in order to ensure good practice and identify any emerging issues of concern. The PI will determine whether the study should be modified based on these findings.

Quality assurance activities include following written and consistent procedures. Data collection pages will be reviewed monthly to ensure the quality of the data collection, management, and analysis.

The study sponsors recognize the requirement to adhere to HIPAA. As stated, all participant PHI will be stored in our HIPAA compliant database with access limited to CIONIC study staff. Additionally, individual data will not be publicly disclosed. In the future, aggregate data from the study (mean, variance, demographic data) may be used to disseminate the results.

Data Storage and Contact for Future Studies

In the informed consent document, participants will indicate whether they would like their information to be saved for future studies. If they select "Yes", their information will be saved. If they select "No," their information will be destroyed from all databases. Study records and study data will be kept indefinitely or until users request they be deleted.

Debriefing Procedures

At the beginning of each lab visit, there will be a debriefing with the participants, where they will be informed of assessments to complete. At the end of the lab visits, subjects may provide feedback about the Cionic Neural Sleeve system.

Costs to Participants

Participants will not be charged and will not incur any costs for participating in the study.

Compensation for Participation

Participants will be given a $50.00 Amazon gift card at the end of the study. If the participant does not complete the entirety of the study, the subject will not receive a $50.00 Amazon gift card.

Reimbursement for Travel Expenses

Transportation logistics (including parking, ride scheduling, and directions) will be communicated by the PI prior to the lab visits. Transportation costs will be reimbursed. If needed, parking cost will be reimbursed by cash or Venmo at the end of the session. Documentation of transportations costs may be requested.

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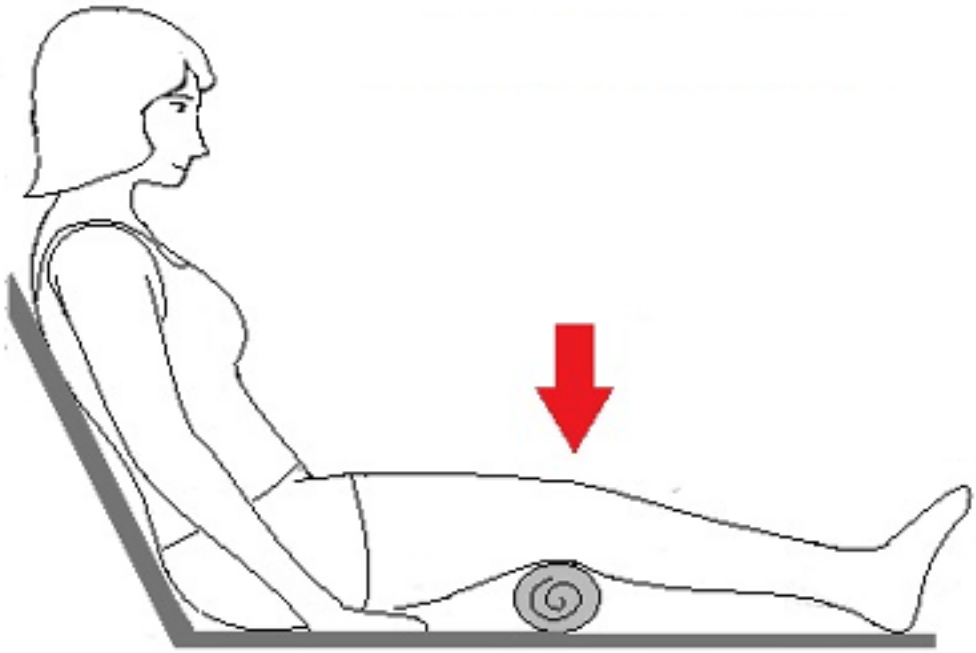
Appendix A: Power Analysis

Power and Significance Level

These are set to standard,
Power = 0.8
Significance Level (alpha) = 0.05

Metric	Effect Size used in calculation	Required sample size when comparing participants' sessions (paired sample)	Required sample size when comparing group A to group B
WOMAC - Function bivariate	0.71[27]	18	32
WOMAC - Pain bivariate	0.41[27]	49	94
WOMAC - Function Standing/Walking bivariate	0.45[27]	41	78

Appendix B: Exercise Handout and Calendar



- You will need a rolled-up towel for this exercise.
- Sit with your leg straight in front of you and placed the rolled-up towel behind the knee.
- Flex your thigh muscle to push your knee down on the towel without lifting your foot off the floor/bed.
- Hold this contraction for 3 seconds and then relax for 3 seconds.
- Repeat 10 times, or as instructed.

WEEK 1

MON	TUE	WED	THURS	FRI	SAT
☐ **Quad exercise: 1 set of 10 reps** ☐ Walk: 10 min	☐ **Quad exercise: 1 set of 10 reps**	☐ **Quad exercise: 1 set of 10 reps** ☐ Walk: 10 min	☐ **Quad exercise: 1 set of 10 reps**	☐ **Quad exercise: 1 set of 10 reps** ☐ Walk: 10 min	*REST*

WEEK 2

MON	TUE	WED	THURS	FRI	SAT
☐ **Quad exercise: 1 set of 10 reps** ☐ Walk: 10 min	☐ **Quad exercise: 1 set of 10 reps**	☐ **Quad exercise: 1 set of 10 reps** ☐ Walk: 15 min	☐ **Quad exercise: 1 set of 10 reps**	☐ **Quad exercise: 1 set of 10 reps** ☐ Walk: 15 min	*REST*

WEEK 3

MON	TUE	WED	THURS	FRI	SAT
☐ **Quad exercise: 1 set of 10 reps** ☐ Walk: 15 min	☐ **Quad exercise: 1 set of 10 reps**	☐ **Quad exercise: 1 set of 10 reps** ☐ Walk: 15 min	☐ **Quad exercise: 1 set of 10 reps**	☐ **Quad exercise: 1 set of 10 reps** ☐ Walk: 15 min	*REST*

WEEK 4

MON	TUE	WED	THURS	FRI	SAT
☐ **Quad exercise: 2 sets of 10 reps** ☐ Walk: 15 min	☐ **Quad exercise: 2 sets of 10 reps**	☐ **Quad exercise: 2 sets of 10 reps** ☐ Walk: 15 min	☐ **Quad exercise: 2 sets of 10 reps**	☐ **Quad exercise: 2 sets of 10 reps** ☐ Walk: 15 min	*REST*

WEEK 5

SUN	MON	TUE	WED	THURS	FRI	SAT
REST	☐ **Quad exercise: 2 sets of 10 reps** ☐ Walk: 15 min	☐ **Quad exercise: 2 sets of 10 reps**	☐ **Quad exercise: 2 sets of 10 reps** ☐ Walk: 15 min	☐ **Quad exercise: 2 sets of 10 reps**	☐ **Quad exercise: 2 sets of 10 reps** ☐ Walk: 20 min	*REST*

WEEK 6

SUN	MON	TUE	WED	THURS	FRI	SAT
REST	☐ **Quad exercise: 2 sets of 10 reps** ☐ Walk: 20 min	☐ **Quad exercise: 2 sets of 10 reps**	☐ **Quad exercise: 2 sets of 10 reps** ☐ Walk: 20 min	☐ **Quad exercise: 2 sets of 10 reps**	☐ **Quad exercise: 2 sets of 10 reps** ☐ Walk: 20 min	*REST*

WEEK 7

SUN	MON	TUE	WED	THURS	FRI	SAT
REST	☐ **Quad exercise: 3 sets of 10 reps** ☐ Walk: 20 min	☐ **Quad exercise: 3 sets of 10 reps**	☐ **Quad exercise: 3 sets of 10 reps** ☐ Walk: 20 min	☐ **Quad exercise: 3 sets of 10 reps**	☐ **Quad exercise: 3 sets of 10 reps** ☐ Walk: 20 min	*REST*

WEEK 8

SUN	MON	TUE	WED	THURS	FRI	SAT
REST	☐ **Quad exercise: 3 sets of 10 reps** ☐ Walk: 25 min	☐ **Quad exercise: 3 sets of 10 reps**	☐ **Quad exercise: 3 sets of 10 reps** ☐ Walk: 25 min	☐ **Quad exercise: 3 sets of 10 reps**	☐ **Quad exercise: 3 sets of 10 reps** ☐ Walk: 25 min	*REST*

WEEK 9

SUN	MON	TUE	WED	THURS	FRI	SAT
REST	☐ **Quad exercise: 3 sets of 10 reps** ☐ Walk: 25 min	☐ **Quad exercise: 3 sets of 10 reps**	☐ **Quad exercise: 3 sets of 10 reps** ☐ Walk: 25 min	☐ **Quad exercise: 3 sets of 10 reps**	☐ **Quad exercise: 3 sets of 10 reps** ☐ Walk: 25 min	*REST*

WEEK 10

SUN	MON	TUE	WED	THURS	FRI	SAT
REST	☐ **Quad exercise: 2 sets of 10 reps, 2x/day** ☐ Walk: 25 min	☐ **Quad exercise: 2 sets of 10 reps, 2x/day**	☐ **Quad exercise: 2 sets of 10 reps, 2x/day** ☐ Walk: 30 min	☐ **Quad exercise: 2 sets of 10 reps, 2x/day**	☐ **Quad exercise: 2 sets of 10 reps, 2x/day** ☐ Walk: 30 min	*REST*

WEEK 11

SUN	MON	TUE	WED	THURS	FRI	SAT
REST	☐ **Quad exercise: 2 sets of 10 reps, 2x/day** ☐ Walk: 30 min	☐ **Quad exercise: 2 sets of 10 reps, 2x/day**	☐ **Quad exercise: 2 sets of 10 reps, 2x/day** ☐ Walk: 30 min	☐ **Quad exercise: 2 sets of 10 reps, 2x/day**	☐ **Quad exercise: 2 sets of 10 reps, 2x/day** ☐ Walk: 30 min	*REST*

WEEK 12

SUN	MON	TUE	WED	THURS	FRI	SAT
REST	☐ **Quad exercise: 2 sets of 10 reps, 2x/day** ☐ Walk: 30 min	☐ **Quad exercise: 2 sets of 10 reps, 2x/day**	☐ **Quad exercise: 2 sets of 10 reps, 2x/day** ☐ Walk: 30 min	☐ **Quad exercise: 2 sets of 10 reps, 2x/day**	☐ **Quad exercise: 2 sets of 10 reps, 2x/day** ☐ Walk: 30 min	*REST*

Appendix C: Encouragement During 6-Minute Walk Test

After the first minute, tell the patient the following (in even tones): “You are doing well. You have 5 minutes to go.”

When the timer shows 4 minutes remaining, tell the patient the following: “Keep up the good work. You have 4 minutes to go.”

When the timer shows 3 minutes remaining, tell the patient the following: “You are doing well. You are halfway done.”

When the timer shows 2 minutes remaining, tell the patient the following: “Keep up the good work. You have only 2 minutes left.”

When the timer shows only 1 minute remaining, tell the patient: “You are doing well. You have only 1 minute to go.”

Do not use other words of encouragement (or body language to speed up).

Appendix D: Quadriceps Strength Testing

1. With the handheld dynamometer placed distally on the affected leg with the knee in 90 degrees flexion, participants will push against the dynamometer for 5 seconds.
2. Subjects will get two warm-up trials separated by a 1-minute rest period.
3. The first warm up will be 10 repetitions at 50% maximal effort, with contractions to be held for 5 seconds.
4. The second warn up will be 5 repetitions at 70% maximal effort, with contractions to be held for 5 seconds.
5. Subjects will then perform 3 repetitions of maximal effort, separated by two minutes of rest between each.
6. The test will be repeated on the other leg.

Appendix E: Western Ontario/McMaster Universities Osteoarthritic Index (Physical Function)

Think about the difficulty you had in doing the following daily physical activities due to your knee during the last 48 hours. By this, we mean your ability to move around and look after yourself.

Question: What degree of difficulty do you have?

	None	Mild	Moderate	Severe	Extreme
Descending stairs	☐	☐	☐	☐	☐
Ascending stairs	☐	☐	☐	☐	☐
Rising from sitting	☐	☐	☐	☐	☐
Standing	☐	☐	☐	☐	☐
Bending to the floor	☐	☐	☐	☐	☐
Walking on flat surfaces	☐	☐	☐	☐	☐
Getting in and out of a car, or on or off a bus	☐	☐	☐	☐	☐
Going shopping	☐	☐	☐	☐	☐
Putting on your socks or stockings	☐	☐	☐	☐	☐
Rising from the bed	☐	☐	☐	☐	☐
Taking off your socks or stockings	☐	☐	☐	☐	☐
Lying in bed	☐	☐	☐	☐	☐
Getting in or out of the bath	☐	☐	☐	☐	☐
Sitting	☐	☐	☐	☐	☐
Getting on or off the toilet	☐	☐	☐	☐	☐
Performing heavy domestic duties	☐	☐	☐	☐	☐
Performing light domestic duties	☐	☐	☐	☐	☐

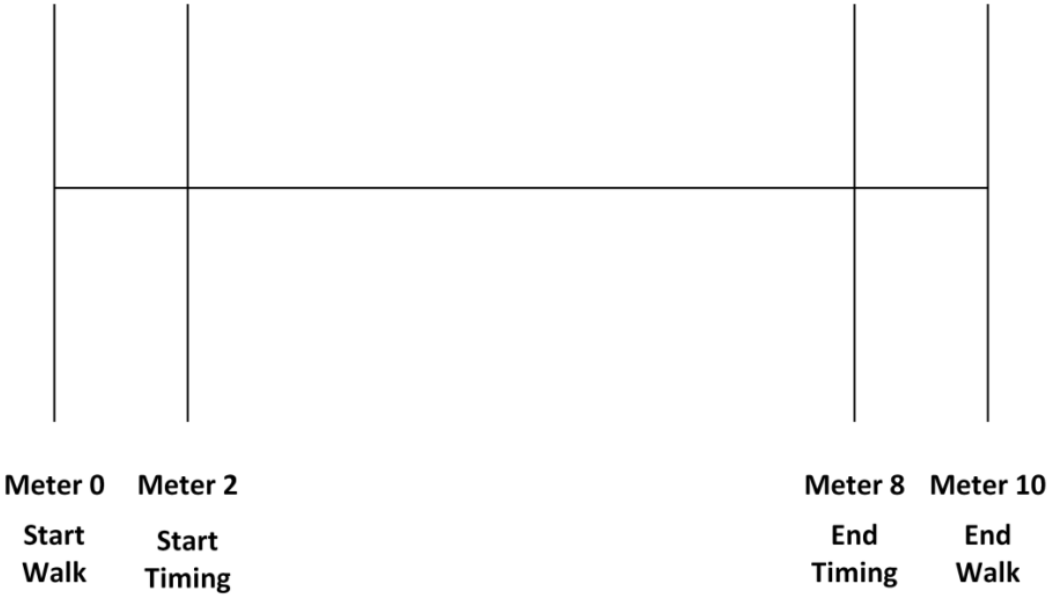
Appendix F: Western Ontario/McMaster Universities Osteoarthritis Index (Pain)

Think about the pain you felt in your knee during the last 48 hours.

Question: How much pain do you have?

	None	Mild	Moderate	Severe	Extreme
Walking on a flat surface	☐	☐	☐	☐	☐
Going up and down stairs	☐	☐	☐	☐	☐
At night while in bed, pain disturbs your sleep	☐	☐	☐	☐	☐
Sitting or lying	☐	☐	☐	☐	☐
Standing upright	☐	☐	☐	☐	☐

Appendix G: 10-Meter Walk Test



1. Subjects will walk with/without assistance for 10 meters.
2. Time will be measured for the intermediate 6 meters to allow for acceleration and deceleration.
3. Timing will start when the toes of the leading foot crosses the 2-meter mark.
4. Timing will stop when the toes of the leading foot crosses the 8-meter mark.
5. Assistive devices can be used but should be kept consistent and documented from test to test.
6. Collect two trials at the subject's comfortable walking speed, followed by two trials at their fast-walking speed.
7. Trials for each speed will be averaged.

Appendix H: 6-Minute Walk Test

1. A “warm-up” period before the test should not be performed.
2. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts.
3. During this time, check for contraindications, and make sure that clothing and shoes are appropriate.
4. Instruct the subject as follows:

   “The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

   You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I’m going to show you. Please watch the way I turn without hesitation.”

   Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

   “Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don’t run or jog.

   Start now, or whenever you are ready.”
5. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
6. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.
7. Record the number of laps from the counter.
8. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance worked, rounding to the nearest meter.
9. Congratulate the patient on good effort and offer a drink of water.

Appendix I: Five Times Sit to Stand Test

1. To perform the test, the person must sit in a chair, with arms crossed over their chest with their back resting on the back of the chair.
2. The chair should have a straight back, and it is recommended it have a height between 43-46 cm.
3. When ordered, the subject should stand up completely and then return to the sitting position during 5 repetitions, performing this activity as fast as possible.
4. Subjects will be timed from the initial sitting position to the final standing position.

Appendix J: Short Form-36

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:

○ Excellent ○ Very Good ○ Good ○ Fair ○ Poor

Compared to one year ago, how would you rate your health in general now?

○ Much better now than one year ago
○ Somewhat better now than one year ago
○ About the same
○ Somewhat worse now than one year ago
○ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
○ Yes, Limited a lot ○ Yes, Limited a Little ○ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Lifting or carrying groceries
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing several flights of stairs
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing one flight of stairs
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Bending, kneeling, or stooping
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking more than a mile
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking several blocks
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking one block
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Bathing or dressing yourself

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

○ Yes ○ No

Accomplished less than you would like

○ Yes ○ No

Were limited in the kind of work or other activities

○ Yes ○ No

Had difficulty performing the work or other activities (for example, it took extra effort)

○ Yes ○ No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

○ Yes ○ No

Accomplished less than you would like

○ Yes ○ No

Didn't do work or other activities as carefully as usual

○ Yes ○ No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

○ Not at all ○ Slightly ○ Moderately ○ Severe ○ Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

○ None ○ Very Mild ○ Mild ○ Moderate ○ Severe ○ Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

○ Not at all ○ A little bit ○ Moderately ○ Quite a bit ○ Extremely

CIONC

CIONC FOR ORTHOPEDICS

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Have you been a very nervous person?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Have you felt calm and peaceful?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Did you have a lot of energy?
- ○ All of the time
- ○ Most of the time
- ○ A good Bit of the Time
- ○ Some of the time
- ○ A little bit of the time
- ○ None of the Time

Have you felt downhearted and blue?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

I am as healthy as anybody I know
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

I expect my health to get worse
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

My health is excellent
Definitely true | Mostly true | Don't know | Mostly false | Definitely false