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Project Narrative for Prospective Research

1) Investigator

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2) Protocol Title

Evaluating wearable assistance on gait biomechanics

3) Objectives

The overarching goal of this study is to improve mobility in individuals with movement disorders through advances in wearable assistance (i.e. powered orthoses). This goal will be accomplished by focusing on two specific research aims. The first aim is to quantify how the magnitude of powered plantar-flexor assistance affects the energetics and mechanics of walking at self-selected (over-ground) and set (treadmill) speeds, and stair ascent in cerebral palsy (CP). The second aim is to evaluate how training frequency and patient characteristics affect clinical and biomechanical gait outcomes across repeated over-ground walking sessions with powered ankle assistance in CP.

4) Background

Neurological deficits, such as those caused by stroke, spinal cord injury, and cerebral palsy, often lead to reduced walking ability and pathological gait patterns that limit quality of life [1-3]. Achieving and maintaining independent mobility for the estimated 17 million individuals with walking disabilities in the US is an essential rehabilitation challenge [4]. Currently, standard-of-care treatments are not fully effective in restoring gait function. Physical therapy, treadmill-based gait training, and intensive muscle strengthening programs have demonstrated variable and inadequate success for gait rehabilitation [5-7]. Research suggests that the type and dosage of standard therapy programs are insufficient for large sustainable gains [8].

Wearable assistive devices (i.e. powered orthoses) offer a promising new means to improve gait rehabilitation outcomes and meet the increasing demand for therapy from our aging population [9]. By administering appropriately timed assistance to lower-extremity joints, powered orthoses can augment weak or deficient muscles to improve walking capacity. Importantly, powered orthoses offer the ability to increase the dosage of gait therapy by providing daily assistance at home and in the community.

The PI (Dr. Lerner) and his colleagues at the National Institutes of Health (NIH) led an exploratory clinical study that sought to evaluate the potential for a powered knee orthosis to treat walking deficits in children and adolescents (ages 5-19) caused by cerebral palsy. The results from the 6-visit 12-week study were very promising with the participants exhibiting significantly improved gait function with the aid of a powered knee orthosis [10, 11]. The success of this previous investigation provides the rationale for continued research that will lead to the effective implementation of wearable assistive devices for use as a long-term rehabilitation strategy at home and in the

community. Working towards this longer-term goal, the study proposed under this protocol is designed to resolve remaining challenges that must be addressed, including:

1) **Improving walking performance:** Pathological gait patterns drastically increase the metabolic requirements for locomotion [18], leading to a barrier to physical activity and downward spiral that results in a deterioration of walking ability with age, ultimately leading to a loss of ambulation in a large portion of the affected population [19]. This study seeks to meet the need to evaluate the use of wearable assistive devices for improving mobility in individuals with movement disorders.

5) Lay Summary (approximately 400 words)

Many individuals with physical disabilities exhibit abnormal walking patterns that limit quality of life and lead to long-term health consequences. Reduced physical activity from gait dysfunction can lead to a downward spiral that results in a deterioration of walking ability with age, ultimately leading to a loss of ambulation in a large portion of the affected population.

The goal of this research protocol is to improve mobility in these individuals with gait disorders through advances in wearable assistive devices. We seek to improve independent walking ability and increase daily physical activity for individuals with cerebral palsy. To meet this goal, our proposal aims to evaluate the novel use of powered ankle assistance from a wearable exoskeleton to improve walking economy across varied terrain.

The knowledge gained from this protocol will enhance our ability to optimize the prescription of powered orthoses for rehabilitation of pediatric and adult gait disorders. Further, this proposal was designed to lay the foundation for our future, long-term research objectives, which is to conduct longitudinal studies (12-36 months) to implement assistive-device interventions to treat neuromuscular gait disorders at home and in the community.

6) Setting of the Human Research

The proposed research will take place at NAU's Flagstaff and Phoenix Biomedical Campuses. At the Flagstaff location, the research will be conducted at or around the new state-of-the-art human performance lab, a 2700 sq. ft. interdisciplinary facility located in the Learning Resource Center (Building 61). At the Phoenix Biomedical campus, the research will be conducted at or around the motion capture facility in NAU's Phoenix Physical Therapy Department.

7) Resources available to conduct the Human Research

NAU's Disability Resources office will assist in participant recruitment. Investigators on this protocol in NAU's department of physical therapy (e.g. Dr. Tarang Jain) will assist Dr. Lerner in the consenting and evaluation of participants with disabilities. Investigators in physical therapy (e.g. Dr. Andrea Lerner) will also assist in patient monitoring during the study visits. Graduate students in Dr. Lerner's Biomechatronics Lab will provide technical assistance and conduct data analysis. All persons assisting with this study will be undergo CITI human subjects and CPR training.

The Flagstaff and Phoenix motion analysis labs contain all of the biomechanics equipment necessary for the experimental measurements. This equipment includes a 10 camera Vicon motion capture system, Bertec instrumented treadmill. Wearable assistive technology, EEG and metabolic measurement equipment will be made available from Dr. Lerner's faculty start-up package.

8) Study Population

a) Inclusion and Exclusion Criteria

Subject population will include:

- 10 individuals with a neurologically-based walking disorder due to cerebral palsy. We will recruit 11 individuals anticipating a 10% withdrawal rate to obtain the target sample size.

Inclusion criteria:

- Age between 5 and 35 years old, inclusive.
- An individual with a diagnosis of a neurologically-based walking disorder due to cerebral palsy.
- Must be able to understand and follow simple directions based on parent report and clinical observation during the history and physical examination.
- Able to provide verbal assent, if appropriate. If the participant is non-verbal, parental interpretation of gesticulation for assent will be used.
- The ability to read and understand English.
- Able to walk at least 30 feet with or without a walking aid (GMFCS Level I-III for individuals with cerebral palsy)
- Able to safely fit into a device configuration and tolerate assistance without knee hyperextension while walking

Exclusion criteria:

- Any neurological, musculoskeletal or cardiorespiratory injury, health condition (including pregnancy), or diagnosis other than cerebral palsy that would affect the ability to walk as directed for short periods of time.
- Participant or parent report that the perspective participant's physician has recommended that they not engage in moderate intensity walking exercise.

Note: No exclusions will be made on the basis of race, gender or ethnic background and efforts will be made to recruit underrepresented minorities.

b) Vulnerable populations

The Human Subjects research includes children and adults with neurological disorders. Several safeguards are included in our protocol to protect their rights and welfare. A

licensed physical therapist or trained safety advocate will be present during all walking trials; the primary purpose of this individual is to ensure participant safety and to be the participant advocate. Walking trials will be immediately stopped upon request of the participant or therapist. Children will be supervised at all times during the test procedures.

A participant's risk for falling during the walking trails will be assessed by a physical therapist; participants who are at risk of falls will be protected by a gait belt or safety harness. Note: the risk of falling from the potential participants as a result of their motor deficits does not represent an elevation of risk beyond those during their daily lives.

Dr. Lerner has over 9 years of experience and training in conducting biomechanical evaluations of gait disorders in individuals of all ages, including children as young as 5 years old. Additionally, he has successfully led multiple pediatric gait analysis studies. The most relevant (and recent) experience includes a clinical study evaluating powered assistance for children with cerebral palsy at the National Institutes of Health. This study was conducted with 7 individuals ages 5-19, and included 6 study visits; the study results were overwhelmingly positive.

9) COVID-19 Mitigation Strategy

COVID-19 may be spreading within our communities for some time. To maximize the safety and health of our participants and research team, the following mitigation techniques will be in place:

a) We will minimize face to face contact by conducting the consent process, when applicable and any possible screening/history questionnaires over the phone. We will also offer the option for participants to complete walking exercises (without the orthosis) at home.

b) The research team will follow CDC guidelines, including wearing face coverings and gloves, when recommended.

c) We will offer face coverings and gloves to visitors (participants and/or their families).

d) We will increase our rigorous sanitation procedure to include wiping down every surface touched by visits to the lab.

10) Recruitment Methods and Consenting Process

a) Recruitment Process:

Participants with gait disorders: We will contact NAU's Disability Resources office by phone or email to discuss our recruitment efforts for participants with stroke, spinal cord injury, Parkinson's disease and cerebral palsy. We will ask them to display our recruitment flyer. We will also provide them with our email/phone recruitment script, that they may use if they choose to contact individuals who they believe may be eligible for participation in our study. Additionally, we will contact clinical care providers, biomedical researchers, physicians or physical therapists by phone or email to discuss our recruitment efforts for this study. If they

are willing to help our efforts, we will mail or email a flyer that they can provide to potential participants. The flyer briefly describes the study, the inclusion and exclusion criteria, and whom to contact for more information. A copy of this flyer is included in the appendix 1. The information on the flyer will also be made available on our laboratory's website. A link to the website has been provided in the recruitment appendix for IRB reference, but the website will not be made available to the public until IRB approval has been obtained. We may also display the flyer throughout hospitals, physician offices, rehabilitation settings, in the community (i.e., schools, churches, local support groups), or posted in print and online newsletters and newspapers after permission for posting is obtained.

Timeline: Recruitment will be staggered so that less than 10 participants will be enrolled at any one time. Therefore, recruitment will take place throughout the duration of the protocol.

Pre-screening: Inclusion/exclusion criteria will be reviewed with each prospective participant (or the parent/guardian in the case of a child) using the pre-screening email or phone scripts (a copy can be found in the appendix 1). Data will not be recorded during the pre-screening process; therefore, pre-screening data cannot and will not be used in the research for either successful enrollees or for screen failures.

b) Informed Consent:

The consent process will take place in person or over the phone in a private, soundproof room by a member of the research team. Consent will be obtained before any study procedures are done. If eligibility criteria are met, the participant, legally authorized individual (LAR), or a legal guardian in the case of minors will be verbally taken through and be provided an electronic (if phone consenting) or hard copy of the consent form and assent form (for minors) to review. For the case of a subject being represented by a LAR, both the subject and the LAR will be present while the consent process. If the subject indicates a willingness to participate via verbal or gesticulated assent, the LAR will sign the consent form on their behalf. Any questions will be answered. The consent form will be provided in English. Once consent and assent are obtained in writing and prior to undergoing any research assessments, all enrolled patients will have their relevant medical history recorded and physical examination completed ("history and physical", Appendix 2). The medical history may be recorded over the phone as well if the participant or guardian is willing to share that information over the phone. The physical will be performed by a licensed physical therapist and relevant medical information such as having a seizure disorder, other current medications, presence of any communicable diseases and allergy history will be documented. Each participant will be screened for any cardiorespiratory, neurological or musculoskeletal contraindications to short exercise bouts of walking or moving lower limbs.

Minor assent will be obtained after parental consent has been provided. The minor assent process is detailed in Appendix A, Children.

11) Procedures involved in the Human Research

Project Narrative for Prospective Research

Overview: Participants with gait deficits will be asked to complete up to 18 visits (they may agree to fewer visits or withdraw at any point). We may terminate a subject's participation if they no longer meet eligibility requirements or if there are safety concerns that cannot be addressed. The experimental conditions allocated during each visit (defined below) will be customized for each participant using the "Visit Allocation" table provided in the consent form and will depend on their specific neurological deficit and walking ability.

Powered Orthosis: Wearable assistance will be provided from powered orthoses that are tailored to the specific gait deficits of each participant (e.g. Fig. 4). The devices provide a small amount of motorized assistance that is intended to augment existing muscle activity to elicit function changes at the ankle joints. This and other similar investigational devices have been classified by the Food and Drug Administration (FDA) as a nonsignificant risk because they do not meet the definition of a significant risk under 812.3(m) of the investigational device exceptions regulation (21 CFR 812) (letter from FDA outlining exemption from Dr. Lerner's prior work at NIH, Appendix 3). This information has been provided to assist the IRB in its determination for this study. Several safety precautions will be implemented to ensure patient safety, including mechanical "stops" to prevent hyperextension of joints, an emergency stop button that shuts off power to the device, and embedded software mechanisms that shut off power if the user were to fall.

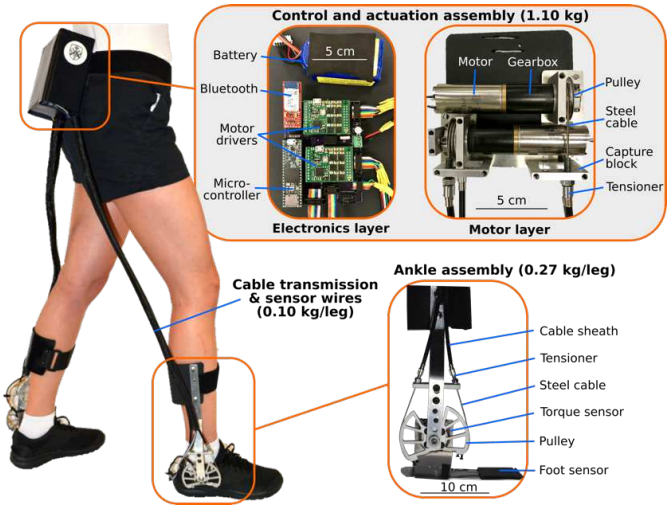

Figure 1. Picture and schematic of a powered orthosis, designed and implemented by Dr. Lerner and the Biomechatronics Lab at NAU.

Unpowered Orthosis: Wearable assistance will be provided from passive orthoses that are tailored to the specific gait deficits of each participant (e.g., ankle-foot orthosis or AFO). These devices are considered less risk than that of powered orthoses.

Experimental conditions: Several powered orthosis conditions will be tested during several modes of walking throughout the course of the study. Trials will take place over-ground and/or on a treadmill. Balance trials will take place on a treadmill. Participants with gait deficits will walk for up to 40 minutes. Frequent breaks will be provided between trials and conditions to avoid fatigue; a maximum of 15 minutes of continuous walking will take place between breaks.

1) Level walking over ground
2) Level walking on a treadmill
3) Walking at a mild incline/decline (0°-15°) on the treadmill
4) "Walking" on a stepmill machine
5) Walking on stairs
6) Balance on a treadmill
7) All terrain walking over ground

8) Mobility analysis

Orthosis Conditions:

1) *Walking without assistance*: We will obtain the normal/representative walking pattern of each participant. This condition will be used to compare the effectiveness of the assistive conditions.
2) *Walking with powered orthosis assistance*: We will provide on/off assistance during walking, depending on the individual's specific gait deficits.
3) *Walking with adaptable powered orthosis assistance*: We will provide assistance that changes magnitude based on measures of gait performance.
4) *Walking with passive (unpowered) orthosis assistance.*

In Laboratory Mobility analysis:

To assess mobility, participants will undergo the following tests, with or without a powered orthosis, under direct supervision by a research team member, who will be available to spot for safety (heart rate and metabolic cost may be collected):

1) Timed up and go: participants will walk as quickly as possible in a safe and controller manner to a cone 3 meters away, turn around, walk back to the chair and sit down; 3 – 6 trials will be collected.
2) 6 minute walk test: participants will walk as quickly as possible in a safe and controlled manner for 6 minutes to test walking endurance; 1 – 3 trials will be collected.
3) Stair test: participants will climb 1 – 4 flights of stairs (with hand rails for support) as quickly as possible in a safe and controlled manner; 1 – 4 trials will be collected.

All terrain walking over ground:

Participants will be monitored and accompanied at all times by the trained safety advocate and study staff during indoor or outdoor all terrain walking trials that may take place on campus in controlled environments. Trials will include ambulation with and without wearable assistance. On-campus locations will include the Engineering, Business, and Learning resource Center buildings, the north and south quads, and campus walkways and urban trails.

Data Collection: Experimental data collection will include motion capture (movement and force gait analysis), measurement of muscle activity (electromyography, EMG), and measurement of oxygen consumption/c02 production (metabolic rate).

Physical activity questionnaire: The *Physical Activity Questionnaire for Older Children (PAQ-C) and Adolescents (PAQ-A)*, two questionnaires that have been validated for children and young adults, may be given to participants with the help of a parent/guardian if necessary.

Description of visits for Participants:

Pre-visit phone call: Optional phone call prior to first in-person visit (but after consent) to collect relevant medical history and physical activity questionnaire.

Visit 1: Participants will undergo consent (if not done over the phone), history/physical/activity questionnaire, and orthotic device fitting. Following device fitting,

the participants will undergo baseline gait and mobility analysis, and then practice walking with powered assistance. The expected duration is 3-4 hours.

Visits 2 through (up to a maximum of) 17: On each visit, participants will complete two to four of the experimental powered orthosis conditions and one to six of the experimental conditions, depending on their customized experimental plan and walking ability. The expected durations are 2-3 hours.

Final visit: On the final visit (maximum number of visits = 18) participants will complete a follow-up gait and mobility analysis, and evaluation of the experimental conditions. The expected duration is 2 – 3 hours.

Timeline: The participants will be asked to complete 1-4 visits per week for 3-12 weeks. To quantify how high frequency gait training affects walking performance, participants will complete four 20-30 minute ankle exoskeleton assisted walking sessions in one week. To quantify how high frequency gait training affects walking performance, participants will complete two 20-30 minute ankle exoskeleton assisted walking sessions each week for two weeks. To accommodate illness, travel, and scheduling conflicts, the maximum time that a participant can be enrolled in the study is 16 weeks.

12) Cost to subjects

The only cost to the participants is a time commitment for which remuneration will be provided. There will be a maximum number of seventeen visits for volunteers with neuromuscular deficits, and a maximum number of four visits for healthy volunteers. Each visit will be a maximum of 4 hours. Any parking costs will be paid for up front, or reimbursed.

13) Risks to subjects

a. **Gait Analysis:** There is a slight risk of falls during ambulatory activities performed during this protocol, but this risk is not greater than during normal daily life. This risk will be minimized by supervision from a licensed physical therapist or trained safety advocate. If the subject appears unstable, a safety harness will be used to arrest any falls that may occur. Therefore, the risk should be no greater than that of normal daily activities. The safety harness will always be used during the incline/decline treadmill walking, stepmill walking, and stair ascent/decent walking.

b. **Walking with wearable Assistance:** The powered and unpowered wearable assistive devices have been evaluated by the FDA as non-significant risks to human subjects (Appendix 3). There is a mild risk of falling when subjects are walking with motorized assistance; subjects may feel a slight perturbation from the orthotic device. The device is not designed or able to over-power the user. Safety measures are integrated within the control algorithms used to control the wearable device such that it automatically deactivates during gait disturbances. During laboratory testing, a physical therapist or trained safety advocate will closely monitor each subject while walking with assistance. If the subject appears unstable, a safety harness will be used to arrest any falls that may occur. Additionally, a therapist or researcher may hold an

emergency switch so the wearable assistance can be immediately deactivated, if needed. For any home/community testing, the participant and parent/guardian (if applicable) will complete extensive training on operation and use of the device.

There is a small risk of pressure by the orthotic braces causing skin irritation. A physical therapist or trained safety advocate will be with the subject throughout the tests, and continuously monitor subject tolerance and inquire about presence of pain, pressure or other complaints to detect any discomfort during testing. If the subject experiences anything beyond minimal discomfort (extra inertia and resistance against movement), we will stop the testing and readjust the device as needed until the problem is resolved. Redness or any other skin problem due to the brace will be inspected at the end of every visit.

c. **Balance with/without Assistance:** There is a small risk of falling during the balance test, but no greater than that of during the walking test. A safety harness will be used to arrest any falls that may occur. A physical therapist or trained safety advocate will stand by the side of the participant and "spot" them.

d. **Muscle Activity Measurement (EMG):** There is minimal risk associated with EMG recording. Small, matchbox sized boxes will be place on various leg muscles to measure when they are active using an electromyography (EMG) device that measures the electrical activity that can be recorded during muscle contractions.

e. Metabolic Testing: There is minimal risk associated with heart-rate monitoring or open-circuit respirometer recording. A facemask covering the nose and mouth that is connected to a respirometer will capture breath inhalation/exhalation.

14) Potential benefits to subjects and/or society

Benefits to Subjects: Walking remains prohibitively challenging for the target population. Properly implemented wearable assistance has a strong potential to improve their ambulatory ability and balance. These studies will determine if wearable assistance is a viable treatment strategy for each of our participants, which can be used to guide future treatment and therapy.

Benefits to Society: Achieving and maintaining independent mobility for the estimated 17 million individuals with walking disabilities in the US is an essential rehabilitation challenge. The proposed studies have the potential to improve gait rehabilitation outcomes and meet the increasing demand for therapy from our aging population. Our findings will provide generalizable knowledge about the optimal assistance for a range of neurological walking disorders. Additionally, our objectives will advance knowledge regarding muscle and brain activation patterns during assisted locomotion, which can advance their use for clinical and research applications.

15) Provisions to protect the privacy of subjects and the confidentiality of data

a) Protection of subject privacy:
Only IRB approved methods and documents will be used for subject recruitment and consent.

b) Protection of data confidentiality:

Samples and data will be stored using codes that Dr. Lerner will assign. Only Dr. Lerner will have the code, which will be recorded in a secure password protected document that will be destroyed 5 years after the completion of the study. Data will be kept in password-protected computers. Hard copies of data will be kept in locked storage on NAU's campus. Only study investigators will have access to the data. Digital pictures and videos will be recorded of participants in this study in conjugation with motion analysis of gait. Participants can choose to sign an Authorization for Recording, Filming, and/or Photographing of Patients (included in the consent form) to give permission to use these videos for publications and public presentations of this work, with or without obscuring identifying features. After the recommended 5 year minimum time frame, all identifying information will be destroyed by erasing files and shredding documents.

16) Subject compensation

Subjects will receive monetary compensation for their participation in the study. All participants will be compensated $30 per hour for lab visits; payment will be made to the parents/legal guardians of minor participants. The minimum compensation for each visit is $30, should the participant or investigator choose to stop the study within the first hour, and the maximum is $120. For those with gait deficits who complete all visits, the maximum possible compensation would be $2160 if they complete all data collection and the visit durations all last 4 hours. Impaired participants will be provided $10 of travel compensation for every 25 miles traveled to the facility where the study will take place, with a maximum of $60 per visit. Impaired participants may be reimbursed up to $120/night of hotel or Airbnb accommodations if an overnight stay is necessary for participation.

All participants can elect on the timing (payment at the end of the study or after each visit) and method of compensation, either a check in the mail or an Amazon gift card.

17) Monitoring the data for subject safety

A therapist will assess the areas on each participant's lower-limbs under the orthoses for skin irritation and redness. Any discomfort following the removal of the orthoses will be addressed and monitored via phone or email for 24-48 hours.

18) Withdrawal of subjects

Subjects or their parents, if applicable, may withdraw from the protocol at any time. There is no elevated risk for withdrawal. If a participant withdraws from this research project before it is complete, results obtained prior to the subject's withdrawal from the study will be maintained and their privacy will be preserved.

Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.

All participants may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

A subject's participation may be stopped by the investigator if the investigator assesses that the participant is at a safety risk or if they are non-compliant with the research protocol; termination will involve no penalty or loss of benefits to which the subject is otherwise entitled.

There is no consequences of a subject's decision to withdraw from the research. Orderly withdrawal will occur by talking with the principal investigator.

19) Sharing of results with subjects

The adult subjects or the parents of child participants may request a report of the individual's motion analysis results. Copies of any manuscripts reporting on the study's full results will also be provided, when available, upon request.

20) Future use and long-term storage of data or specimens

De-identifiable motion and gait data may be kept for future research. Following publication of our findings, these de-identifiable data will be made available upon request. Dr. Lerner will hold and maintain the repository.

21) Information management

Dr. Lerner is responsible for data management.

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Statistical Analysis Plan (SAP)

Protocol Overview

Following the informed consent process, all participants completed a high frequency gait training protocol followed by a washout period and a low frequency gait training protocol. For each gait training protocol, participants completed a shod (shoes only) pre and post intervention assessment that included walking for at least 6 minutes while we measured speed, energy cost, cadence, step length, and muscle activity.

For the high frequency gait training portion, participants completed four 20-30 minute ankle exoskeleton assisted walking sessions in one week. For the low frequency gait training portion, participants completed two 20-30 minute ankle exoskeleton assisted walking sessions each week for two weeks. During the walking sessions, plantar flexor exoskeleton assistance was initially set to 0.35 Nm/kg and adjusted as need to prevent knee hyper extension. A small amount of dorsiflexor assistance was provided to address drop foot (1-2 Nm), as needed.

Outcome Measures

Our primary outcome measures are the metabolic energy required to walk and walking speed. Our secondary outcome measures are stride length, cadence, and muscle activity variance ratio.

Statistical Analyses

- We calculated the percent change in each outcome measure pre and post each ankle exoskeleton assisted gait training frequency (high frequency and low frequency) for each participant.
- We computed the group mean and standard deviation for each outcome measure.
- We then calculated the difference in the percent changes between the two frequencies.
- We then tested whether these data were normally distributed using the Shapiro-Wilk normality test. We found that all data were normally distributed.
- We used paired two-tailed Student's t-tests to compare the outcome measures between high frequency and low frequency gait training.