Protocol for

Effects of a Soft Robotic Exosuit on Exercise Capacity, Biomarkers of Neuroplasticity, and Motor Learning after Stroke

NCT05138016

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BU Charles River IRB
Application Form (Full Board and Expedited

Review)SECTION A: PROTOCOL AND CONTACT

INFORMATION

Protocol Number (To be assigned by IRB Office):	4977E
Protocol Title:	Effects of a Soft Robotic Exosuit on Exercise Capacity, Biomarkers of Neuroplasticity, and Motor Learning after Stroke
Principal Investigator **(Name, degrees, licenses, etc.):** ☐ Mr. ☐ Ms.	Louis Awad, PT, DPT, PhD
Department/School:	Department of Physical Therapy & Athletic Training; College of Health and Rehabilitation Sciences: Sargent College
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Additional Contact Person:	Anna Roto, MS, MPH
Email:	aroto@bu.edu
Telephone:	860-428-6301 (personal cell); 617-500-3645 (lab google number)
☒ YES **(REQUIRED)**	I confirm that I qualify to serve as the Principal Investigator of this study and am in compliance with the following policies: http://www.bu.edu/researchsupport/compliance/human-subjects/

SECTION B: FUNDING

Provide information regarding **ALL** funding sources for this project, including existing funding, pending funding, and funding that has been applied for to support this research.

Please check all that apply:	
☒	This research is funded
☐	Funding has been requested Have you received Just In Time (JIT) Notification? ☒ Yes ☐ No NOTE: Once the funding has been awarded, submit an amendment to the IRB to add the funding source
☐	Research is not funded

If the research is funded or funding has been requested, it is REQUIRED that you completethe box below. If you don't have an award #, please state that in the box below.
If you have multiple funding sources, add additional boxes as necessary.

Sponsor Name	American Heart Association
Title of Grant/Proposal	Soft Robotic Exercise Intervention for Enhancing Neuroplasticity After Stroke

Sponsor Award # **(REQUIRED)*** *If Award is pending, put "pending".		19PRE34430087
YES	**NO**	
☒	☐	Is Boston University the Prime Awardee of the grant?
☐	☒	Is Boston University receiving a sub-award? Name of Prime Recipient:
☐	☒	Is the research being supported by an Industry Contract or Clinical Trial Agreement?

***NOTES:**

- Provide a copy of the grant application, funding proposal, contract/agreement, scope of work, or sub-award agreement supporting the research. If an award is pending, once the funding has been awarded, submit an amendment to the IRB to add the funding source.
- If this research study is for your dissertation, provide a copy of your prospectus (if available).

SECTION C: CONFLCT OF INTEREST

☒ YES **(REQUIRED)**	I confirm that **ALL** those responsible for the design, conduct, or reporting of the proposed research, including at minimum, all Senior/key personnel in the grant application, have completed the financial interest disclosure forms, submitted them to the COI office, and completed training as dictated at: http://www.bu.edu/researchsupport/compliance/conflicts-of-interest/, and as provided under *the Boston University Investigator Conflicts of Interest Policy for Research.* **NOTE: You must attach a copy of the PI's COI submission confirmation email. COI submission confirmation emails for all other study staff should be maintained at the research site.**
Of the financial interest disclosure forms submitted, did you check "yes" to any of the questions on either the FIND1 or NONFIND1 form? ☐ Yes* ☒ No	

***If you checked "yes" to any of the questions on either the FIND1 or NONFIND1 form, the IRB Director will contact the COI office to obtain the disclosure information.**

SECTION D: TYPE OF REVIEW

For Guidance regarding Type of Review please refer to the CRC IRB website

I. **FULL BOARD ☒**
Please refer to the CRC IRB website for Full Board submission deadlines and meeting dates.

II. **EXPEDITED ☐**
In order to qualify for expedited review, the study must be no more than minimal risk* **AND** must fall into one of the categories below. Check all that apply:

1. ☐ Clinical studies of drugs and medical devices only when an investigational new drug application (IND) or investigational device exemption application (IDE) is not required

2. ☒ Collection of blood samples by finger stick, heel-stick, ear stick, or venipuncture as follows:
   a. From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or
   b. From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.

3. ☒ Prospective collection of biological specimens for research purposes by noninvasive means. Examples include hair and nail clippings, saliva or cheek swabs, sweat, etc.

4. ☒ Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. Examples:
   - Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy
   - Weighing or testing sensory acuity
   - Magnetic resonance imaging
   - Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography
   - Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual

5. ☐ Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis)

6. ☒ Collection of data from voice, video, digital, or image recordings made for research purposes.

7. ☐ Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Note: The IRB will make the final determination on the Type of Review

***Minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

SECTION E: STUDY STAFF AND HUMAN SUBJECTS TRAINING

List **ALL** current members of the research team in the table below. Add more rows as necessary.

STUDENT RESEARCH:
The Faculty Advisor must be listed as a co-investigator in this section and must complete the Human Subjects training requirements. Faculty Advisors are responsible for reviewing the IRB application, agreeing to serve as the Co-PI for this study with the student and are responsible for the ethical conduct of this student's human subjects research. Faculty Advisors must sign this Application prior to it being submitted to the IRB.

BU CHARLES RIVER CAMPUS (CRC) INVESTIGATORS/STUDY STAFF
Note: Boston University Medical Campus (BUMC) investigators/study staff should be listed in the NON-BU INVESTIGATOR/STUDY STAFF section

Name, Degree, Department, School	**Study Role (e.g. co-investigator, research coordinator, research assistant, project manager, lab manager)**	***Training**
Louis Awad, PT, DPT, PhD Department of Physical Therapy and Athletic Training, College of Health & Rehabilitation Science: Sargent College, Boston University	Principal Investigator	☒ CITI Most Recent Date Completed: 01/02/17
Terry Ellis, PhD, PT, NCS Department of Physical Therapy and Athletic Training, College of Health & Rehabilitation Science: Sargent College, Boston University	Co-Investigator	☒ CITI ☐ Other**: HIPAA training completed 9/2/15 Most Recent Date Completed: 6/12/15
Karen Hutchinson, PT, DPT, PhD Department of Physical Therapy and Athletic Training, College of Health & Rehabilitation Science: Sargent College, Boston University	Co-Investigator	☒ CITI Most Recent Date Completed: 06/30/14

Julie Starr, PT, DPT, CCS Department of Physical Therapy and Athletic Training, College of Health & Rehabilitation Science: Sargent College, Boston University	Co-Investigator	☒ CITI Most Recent Date Completed: 04/05/16
Regina Sloutsky Neuromotor Recovery Laboratory	Research Physical Therapist	☒ CITI Most Recent Date Completed: 05/04/17
Teresa Baker Neuromotor Recovery Laboratory	Research Physical Therapist	☒ CITI Most Recent Date Completed: 08/03/20
Anna Roto Neuromotor Recovery Laboratory	Project Manager Research Assistant	☒ CITI Most Recent Date Completed: 08/28/17
Andy Alvarez Neuromotor Recovery Laboratory	Research Assistant	☒ CITI Most Recent Date Completed: 07/28/17
Macauley O'Connor Neuromotor Recovery Laboratory	Research Assistant	☒ CITI Most Recent Date Completed: 12/24/17
Ashlyn Aiello Neuromotor Recovery Laboratory	Research Assistant	☒ CITI Most Recent Date Completed: 04/16/18
Ashley Collimore Neuromotor Recovery Laboratory	Research Assistant	☒ CITI Most Recent Date Completed: 06/13/18
Ellie Ottman, PT, DPT Neuromotor Recovery Laboratory	Research Physical Therapist	☒ CITI Most Recent Date Completed: 7/12/19
Lillian Ribeirinha-Braga Neuromotor Recovery Laboratory	Research Assistant	☒ CITI Most Recent Date Completed: 7/8/19

- *For more information regarding the Human Subjects Training Policy, refer to the 'Training' section of the Policies & Guidance section IRB website.
- **If the investigator/study staff did not complete CITI, you must submit a copy of his/her training certificate.

NON-BU INVESTIGATORS/STUDY STAFF* ☐ **N/A**

Note: BUMC and BMC staff are considered non-BU staff and should be listed in this section. Add more rows as necessary. All the columns in the box below must be completed. In addition, you must complete the box that follows with a description of the activities for each staff member.

Name, Degree, Institution	Study Role	Staff Information	Will IRB Approval be Obtained from Non-BU Institution?
		1. Will this staff interact with subjects? ☐ Yes ☐ No 2.Will this staff have access to identifiable information? ☐ Yes ☐ No 3.Is the work that the staff will complete related to their role or coursework at their institution.? ☐ Yes ☐ No	☐ Yes; provide copy of IRB approval letter ☐ No (provide reason): The site is not engaged in research.
Qing Mei Wang, MD PhD, Spaulding Rehabilitation Hospital	Co-Investigator	1. Will this staff interact with subjects? ☐ Yes ☒ No 2.Will this staff have access to identifiable information? ☐ Yes ☒ No 3.Is the work that the staff will complete related to their role or coursework at their institution.? ☐ Yes ☒ No	☐ Yes; provide copy of IRB approval letter ☒ No (provide reason): Cede request filed through smartIRB.

*If IRB approval will be obtained from the affiliate site, only list the lead investigator from the affiliate on this form.

The box below must be completed. Include a summary for each staff listed in the above box. If any of the investigators listed on this form are not affiliated with BU, provide a summary of the study activities that he/she will conduct. If IRB approval is not being obtained at the affiliate institution, provide an explanation. **NOTE: Non-BU staff may be required to complete an Individual Investigator Agreement (IIA). The IRB will notify you if this form is required.**

Dr. Qing Mei Wang is the director of the Stroke Biological Recovery lab at Spaulding Rehabilitation Hospital. Dr. Wang is providing laboratory space for blood storage, processing and analysis and will supervise the blood sample analyses conducted by our team.

REQUIRED GOOD CLINICAL PRACTICE TRAINING FOR NIH-FUNDED CLINICAL TRIALS

YES*	NO	NIH-FUNDED CLINICAL TRIALS
☐	☒	Is your study NIH-Funded AND meet the definition of a clinical trial as defined in the NIH policy?

SECTION F: LOCATION OF THE RESEARCH

YES*	NO	
☒	☐	Will this research take place at sites/locations other than Boston University? **Note:** If the research will take place at Boston University, state the location (Building and Room number): Dr. Qing Mei Wang, MD, PhD, the director of the Stroke Biological Recovery Lab at Spaulding Rehabilitation Hospital is providing laboratory space for storage, processing, and analysis of all de-identified blood samples collected for this study. Blood will be stored, processed and analyzed at Spaulding Rehabilitation Hospital on the Charlestown campus, building CNY 79/96, room number 125. The Motional Analysis Lab at Spaulding Rehabilitation Hospital is providing laboratory space for exercise testing and gait training, as well as motion capture and sensor movement data collection. The Motion Analysis Lab is located at Spaulding Rehabilitation Hospital on the Charlestown campus at 300 First Avenue, Room 3297, Charlestown, MA 02129. All participant testing will take place in the Neuromotor Recovery Laboratory at 100 Ashford Street, Boston, MA 02215, or the Motion Analysis Laboratory at 300 First Avenue, Room 3297, Charlestown, MA 02129.

*If **YES,** please complete the boxes below

NOTE: You are responsible for obtaining permission/letters of support for research conducted off-site. This may include locations such as schools, workplaces, community organizations, etc. You must submit the letters/documentation of support with this application.

Institution Name and Address (if known)	**Describe Involvement (recruiting, consenting, data analysis, etc.) of the site. If the site or the site staff is not involved (engaged)[1] in research procedures, state NONE.**	**IRB/Ethics Approval/Site Permission Attached? If no[2], explain the plan to obtain this approval. If the site is not engaged in the research, you do not need to complete the box.**

Spaulding Rehabilitation Hospital, Stroke Biological Recovery Lab Spaulding Rehabilitation Hospital, Charlestown campus, building CNY 79/96, room number 125	NONE.	
Spaulding Rehabilitation Hospital, Motion Analysis Lab Spaulding Rehabilitation Hospital, Charlestown campus, room number 3297	The site may be involved in data collection. Anyone involved in this research from this site is listed in section E.	

[1]Guidance on Engagement of Institutions in Human Subjects Research
[2]If IRB approval will not be obtained at the site, describe the IRB oversight arrangements here:

YES*	NO	
☐	☒	Is the off-site location requesting that the Boston University IRB review the protocol in place of local IRB review? If **YES**, complete the Single IRB Review Form "Boston University is Institution A"

YES*	NO	
☒	☐	Is the BU PI the lead investigator **OR** is BU the lead site for this research? **Note: This box only needs to be completed if the off-site location is engaged in the research.**

*If **YES**, provide the following information in this box:

- The plan for collection and management of data from all the sites
- The plan for reporting and evaluating:
- Unanticipated problems
- Serious and/or continuing non-compliance
- Suspensions and terminations of research
- Interim results
- Protocol modifications
- The name of the Principal Investigator from each site
- If IRB approval will be obtained at the site, confirmation that you have a copy (or will obtain a copy) of the IRB approval letters and the IRB-approved protocols from each site
- If IRB approval will be obtained at the site, confirmation that the site IRB has a FederalWide assurance (FWA)

YES*	NO	
☐	☒	Will this research be conducted outside of the United States?

		If **YES**, complete the International Research Form.

SECTION G: STUDY SUMMARY

Summarize the study in lay language (do not copy from the grant/scope of work/proposal, etc.). This summary should include the research design, purpose, objectives, research question, hypothesis, and any relevant background information.

Do not include a list of citations in this section. Please limit this section to no more than 300 words.

High intensity exercise is known to improve a person's ability to learn new motor skills. The goal of this project is to evaluate if a robotic exoskeleton can help people who have had a stroke perform rehabilitation exercises at higher intensities than they are able to without the exoskeleton. We will measure training intensity, biomarkers of neuroplasticity (eg, brain-derived neurotrophic factor; BDNF), and motor learning ability when people with and without the exoskeleton. In addition, we will use data from this study to help further development of the exoskeleton.

Aim 1: Determine the effects of a soft robotic exosuit on gait training intensity and serum BDNF in persons post-stroke.

Hypothesis 1: We hypothesize that exosuits will allow individuals post-stroke to (i) walk at higher intensities or (ii) walk at a high intensity for longer durations.

Hypothesis 2: We hypothesize that training at a higher intensity, or training at high intensity for longer durations, will result in increased serum brain-derived neurotrophic factor (BDNF).

Aim 2: Determine the effects of a high intensity (HI) exercise intervention enabled by the gait-restorative effects of exosuits on motor learning after stroke.

Hypothesis 3: We hypothesize that a single bout of HI exercise with an exosuit will lead to demonstrably better motor learning during a novel motor learning task than a single bout of HI exercise without an exosuit.

SECTION H: RESEARCH METHODS AND ACTIVITIES

(Check all that apply)

☒	Collection of audio, video, digital, or image recordings
☒	Biological samples □ Complete Biological Samples Form Examples: blood, hair, cheek swab, urine, tears, saliva, etc.
☐	Collection of data that may be sensitive and if disclosed could put subjects at risk for legal or social harms. (e.g. Illegal behaviors, HIV status, psychiatric illness, information related to sexual behaviors, etc.

☐	Coordinating Center/Lead Site
☐	Deception
☒	Devices □ Complete Devices Form
☐	Drugs □ Complete Drugs Form
☐	Ethnographic: The study of people in their own environment through the use of methods such as participant observation and face-to-face interviewing
☐	Focus Groups
☒	Genetics Testing □ Complete Genetics Form
☐	MRI
☐	Placebo
☐	Pregnancy Testing
☒	Randomization
☒	Surveys, interviews, questionnaires
☐	Secondary Data Analysis
☒	Other (please describe): Common clinical examination approaches will be used to measure cognition, sensorimotor function, and walking ability.

SECTION I: PARTICIPANT POPULATION

Provide the Number of Participants to be Enrolled. If you have sub-groups or more than one arm, please separate out these enrollment numbers. Note: Please account for participants who may drop out or be withdrawn from the study. Anyone who signs a consent form is considered to be enrolled in the research regardless of whether they complete any study procedures.
We plant to recruit up to 100 adults in the chronic phase of stroke recovery to participate in this study, with an enrollment goal of up to 40.

Check all categories that apply to your participant population:

☒	Adults
☐	Children (< 18 years of age)
☐	Adults with Limited Decision-Making Capacity
☐	Non-English Speaking
☐	Prisoners
☒	BU Employees
☐	BU Students
☐	Wards of the state
☐	Other (please describe):

If a population other than 'Adults' has been checked, describe the additional safeguards that have or will be put in place to protect those individuals, and provide the rationale for including this population in the research study. For information on additional protections, please see the 'Supplemental Guidance' section of the CRC IRB webpage.
The PI will have no authority over BU employees who may participate.

Eligibility Criteria
Inclusion Criteria: • Diagnosis of stroke • Chronic phase of recovery (>6mo post-stroke) (self-report) • 18-80 years old (self-report) • Independent ambulation (with or without an assistive device) for at least two minutes (confirmed at secondary screening visit) • Provide HIPAA Authorization to allow communication with healthcare provider as needed during the study period • Medical clearance by the participant's physician
Exclusion Criteria: • Score of > 1 on question 1b and > 0 on question 1c on the NIH Stroke Scale (NIHSS) • Inability to communicate • Unexplained dizziness in the last 6 months • Serious comorbidities that may interfere with ability to participate in this research (for example: musculoskeletal, cardiovascular, pulmonary, and neurological – other than stroke)

- Anemia (defined as hemoglobin levels of <13 g/dL for men and <12 g/dL for women)
- Clotting disorders**
- Have given blood to any other entity within 60 days prior to blood collection
- History of significant Peripheral Artery Disease (PAD)
- Unresolved Deep Vein Thrombosis (DVT)
- Uncontrolled or untreated hypertension
- Significant paretic ankle contractures (plantarflexion > 5°)
- Psychiatric or cognitive impairments that may interfere with proper operation of the device
- Presence of open wounds or broken skin at device locations requiring medical management
- Known urethane allergies
- Pregnancy

** Note: We may enroll participants who do not have a clotting disorder, but who are on anti-clotting medications.

SECTION J: RECRUITMENT

Provide a summary of the recruitment process, including who will recruit, when and where recruitment will occur, and how subjects will be identified

Submit all recruitment materials (e.g. advertisements, brochures, flyers, letters/e-mails, scripts, etc.) as separate documents in either Word or PDF format.

All investigators and research assistants will be involved in recruitment. Recruitment may occur via email (using IRB-approved language), IRB-approved flyers, promotional videos, or word of mouth through the following:

1) Clinicians at clinics, centers, and institutions with whom the investigators have developed collaborating relationships may approach patients who they believe may be interested in participating in the study to inform them about the study. These clinicians will not be actively recruiting for the study.
    a) If these patients are interested, they will be provided with a research flyer which they can use to initiate contact with study staff.
2) Clinical research programs at the study site locations keep the contact information of patients who have had a diagnosed stroke and are interested in participating in research.
    a) Potential Study Subjects from these registries will be contacted via email or phone and asked if they wish to learn more about the study. If they are interested, they will be provided with a flyer that they can use to initiate contact with study staff.
3) Clinicians at rehabilitation hospitals, such as Spaulding, and clinics at the study site locations will be provided with IRB-approved recruitment materials that they can make available to their patients.
    a) Patients that are interested can then use the information in these materials to initiate contact with study staff.

4) Study investigators may be invited to speak about the study to relevant organizations, including recreational/social programs, support groups, etc. Study flyers will be left at or provided to these locations for distribution.
    a) Individuals that are interested can then use the information on these flyers to initiate contact with study staff.
5) Information about the study may also be distributed via the following methods with prior approval from site staff/managers:
    a) At local stroke support group meetings and in university or hospital buildings
    b) Relevant programs serving persons with disabilities (e.g. stroke survivor programs, sports or recreational programs)
    c) Relevant newsletters serving people with disabilities
    d) Relevant buildings around study locations, at local businesses (e.g. coffee/sandwich shops), at local health or fitness centers
    e) Relevant websites such as Craigslist or print papers, social media sites or groups (e.g. stroke survivor Facebook groups)
6) Participants previously known to the Boston University through participation or screening in other studies may also be recruited. Participants who have recently participated, or have been screened for other studies at Boston University, may be contacted to determine their interest in participating in this research study. We will only contact participants who have expressed their interest in, and given permission, to be contacted for additional research studies at Boston University. If the participant agrees to participate, information already known to the Boston University may be used to complete the primary and/or secondary screening documentation. Study staff may reach out to participants to fill in any gaps or update information as needed on a case by case basis.

Study Subjects will be identified for enrollment, provided with a brief description of the study (flyer or email) and if interested, will either contact study staff or be contacted by study staff for a ten-minute phone call. During this first conversation, the goals of the study will be clearly described, and the potential Study Subjects will be asked questions to ascertain whether they preliminarily meet the study's inclusion/exclusion criteria (using the Primary Screening Form). This screen will take under ten minutes and will be conducted by the trained study personnel listed in section E. If they remain preliminarily eligible and interested, they will be invited to participate in the subsequent screening study visit.

SECTION K: CONSENT AND ASSENT

Please refer to the consent and assent form templates on the IRB website when creating your consent/assent documents. The templates include the required elements of consent and will help to ensure that your consent/assent form meets the requirements of the federal regulations and the BU CRC IRB.

STUDENT RESEARCHERS must: 1) indicate in the consent form/information sheet/script that he/she is a student and 2) list the Faculty Advisor as a contact in the form/sheet/script.

Provide a summary of the consent process, including who will consent participants, when and where consent will occur. The summary should include, as appropriate, any waiting period between informing the prospective participant about the research and obtaining consent, such that the prospective participant or the legally authorized representative has sufficient opportunity to consider whether to participate, and steps taken to minimize coercion or undue influence. **Submit copies of all consent forms and scripts; materials should be submitted as separate documents in Word format.**
If the participant meets the study criteria and remains interested in participating, they will be scheduled for an in-person secondary screening visit to confirm eligibility. This visit will take place at the Neuromotor Recovery Laboratory located at 100 Ashford Street, Boston, MA 02215. Trained study personnel will conduct the in-person secondary screening visit, which may take up to a maximum of four hours. First, the informed consent document will be reviewed in detail with the participant. The participant will be informed that participation in the study is entirely voluntary and will have no effect on any present or future medical or rehabilitation care. The participant will be encouraged to ask questions about the study to ensure complete understanding of all study elements. All questions will be answered thoroughly. Only when the participant has provided full written informed consent will study personnel proceed with further research activities. Alternatively, pending participant preference, the informed consent process may happen remotely. In this case, informed consent will be conducted virtually through BU Zoom or over the phone. Participants will be emailed the informed consent form to follow along as it is summarized by a research team member. The participant will have the ability to sign the informed consent form virtually, or to print and sign/date the emailed informed consent form, which will be returned to the study staff by email. If the consent form is signed virtually, the signed/dated document will be stored securely on our BU Sharepoint. A version of the signed/dated document will be provided to the participant by direct download, email or in hardcopy at their first in-person visit (participant preference). If possible, the HIPAA authorization will also be reviewed and completed by the participant remotely and emailed to study staff. All of these email communications will be transmitted using BU SecureMail.

Indicate the consent and/or assent process and document(s) to be used in this study. Check all that apply

Consent: Adults (≥18 years old); One of the following MUST apply	**N/A ☐**
☒	Consent Form/Information Sheet
☐	Verbal Consent (Script) **Note:** If written consent will not be obtained, complete the 'Waiver of Written Documentation Consent' box (Box 1) located further down in this section
☐	Consent will not be obtained **Note**: If consent will not be obtained, complete the 'Waiver or Alteration of Consent' box (Box 2) located further down in this section

Assent of Children (≤ 18 years old); One of the following MUST apply **N/A ☒**	
☐	Assent Form **OR** Parent Consent Form/Information Sheet (older children may sign the parent consent form along with their parents as long as the consent form is written at the grade level of the subjects)
☐	Verbal Assent (Script)
☐	Assent will not be obtained; one of the following conditions must exist:
	1. ☐ The capability of some or all of the children is so limited that they cannot reasonably be consulted; 2. ☐ The children are too young to provide assent; 3. ☐ The intervention or procedure involved in the research holds out the prospect of direct benefit to the health or well-being of the children and is available only in the context of the research 4. ☐ The research meets the same conditions as those for waiver or alteration of informed consent in research involving adults, as specified in the regulations at 45 CFR 46.116(d)*. **(Complete the 'Waiver or Alteration of Consent' box (Box 2) located further down in this section)**
Guidance on age requirements for obtaining assent: • **Parental Permission for minors under 6 years old** • **Verbal assent for minors 6-11 years old** • **Written assent from minors ages 12-17 (unless verbal consent is approved for the parents/adult subjects**	
Parental Permission; One of the following MUST apply **N/A ☒**	
☐	Parental Consent Form
☐	Parental Verbal Consent (Script) **Note:** If written consent will not be obtained, complete the 'Waiver of Written Documentation of Consent' box (Box 1) located further down in this section
☐	Parental permission will not be obtained; **one of the following conditions must exist:** 1. ☐ The research protocol is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children). 2. ☐ The research meets the same conditions as those for waiver or alteration of informed consent in research involving adults, as specified in the regulations at 45 CFR 46.116(d)*. **(Complete the 'Waiver or Alteration of Consent' box (Box 2) located further down in this section).**

Consent: Adults with Limited Decisional Capacity to Consent (≥18 years old) N/A ☒ **Describe the consent and/or assent process for enrolling adults with limited decisional capacity to consent to research. Including how decisional capacity will determined, and who will serve as Legally Authorized Representative.**
Assent will be obtained from: ☐ All Subjects ☐ Some participants, specify: ☐ No participants. If no participants will assent, provide a rationale:

☐	Consent will be obtained from the subject's Legally Authorized Representative (LAR) **(REQUIRED).** **Who will serve as LAR:**

CONSENT OF NON-ENGLISH SPEAKING SUBJECTS N/A ☒ **Describe the process for obtaining consent from non-English speaking subjects. List the individual who will serve as the interpreter and his/her qualifications.** **NOTE:** A copy of the translated consent along with the Attestation Form for Translation of Consent must be submitted. The Attestation Form can be located on the IRB website.

BOX 1—WAIVER OF WRITTEN DOCUMENTATION OF CONSENT

WAIVER OF WRITTEN DOCUMENTATION OF CONSENT N/A ☒ **Either Criteria 1 or 2 must be met in order to qualify**	**Yes**	**No**
☐ **Criteria 1**		
The research is **NOT** FDA Regulated	☐	☐

The only record linking the subject and the research would be the consent document	☐	☐
The principal risk would be potential harm resulting from a breach of confidentiality	☐	☐
Each subject will be asked whether the subject wants documentation linking the subject to the research and the subject's wishes will govern	☐	☐
A written statement/information sheet will be provided to subjects. **If NO**, provide rationale for not providing this information:	☐	☐
☐ **Criteria 2**		
The research is **NOT** FDA Regulated	☐	☐
The research presents no more than minimal risk of harm to subjects	☐	☐
The research involves no procedures for which written consent is normally required outside of the research context	☐	☐
A written statement/information sheet will be provided to subjects. If **NO**, provide rationale for not providing this information:	☐	☐
☐ **Criteria 3**		
The research is **NOT** FDA Regulated	☐	☐
The research presents no more than minimal risk of harm to subjects	☐	☐
The subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm	☐	☐
There is an appropriate mechanism for documenting that informed consent was obtained	☐	☐
A written statement/information sheet will be provided to subjects. If **NO**, provide rationale for not providing this information:	☐	☐

BOX 2—WAIVER OR ALTERATION OF CONSENT

NON-FDA REGULATED STUDIES

WAIVER OR ALTERATION OF CONSENT N/A ☒	**Yes**	**No**
45 CFR 46.116 Waiver or alteration of consent. The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents ALL of the criteria listed below:		
The research involves no more than minimal risk to the subjects;	☐	☐
The waiver or alteration will not adversely affect the rights and welfare of the subjects;	☐	☐
The research could not practicably be carried out without the waiver or alteration;	☐	☐
If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;	☐	☐
Whenever appropriate, the subjects will be provided with additional pertinent information after participation. **If NO**, provide rationale for not providing this information:	☐	☐
Provide the justification/rationale for why this study meets the above criteria for waiving or altering consent (REQUIRED):		

FDA-REGULATED STUDIES

Per FDA guidance issued in July 2017, the IRB may waive or alter informed consent requirements for certain minimal risk clinical investigations when the IRB finds and documents ALL of the criteria listed below:	**Yes**	**No**

The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the subjects;	☐	☐
The waiver or alteration will not adversely affect the rights and welfare of the subjects;	☐	☐
The clinical investigation could not practicably be carried out without the waiver or alteration	☐	☐
Whenever appropriate, the subjects will be provided with additional pertinent information after participation. **If NO**, provide rationale for not providing this information:	☐	☐
Additional Comments:		

SECTION L: STUDY PROCEDURES

In the box below provide a detailed description of the study procedures to be performed (preferably in sequential order). Be sure to specify which procedures are for research purposes and which procedures are part of standard of care, if applicable. Be sure to include the following information:

- **Methods of data collection**
- **Details regarding research activities/procedures/interventions**
- **Number, frequency, duration and types of subject contacts (visits, phone calls, internet surveys, mailings, etc.)**
- **Time required from each subject**
- **Use of equipment (eye-tracker, treadmill, sensors, etc.). Provide a brief description of equipment that will be used in the study.***

***Note: The IRB may request more information about the equipment (including equipment manuals) and/or request that you submit Appendix C: Device Form.**

Submit copies of all surveys, interview questions, assessments, screening scripts, etc. that will be used during the conduct of this study; materials should be submitted as separate documents in either Word or PDF format.

Primary Screening

Eligibility will be verified via email or phone, utilizing the Primary Screening Form.

HUMAN SUBJECTS TESTING

- **Secondary Screening Visit**
- **Medical Clearance**
- **Exosuit Fit & Comfort**
- **Maximal Effort Tests**
- **Motor Learning Pilot Study**
- **Gait Training Evaluations**

The maximum number of study visits a participant may be asked to complete is 22. Participants will be asked to participate for a length between 12 weeks and (up to) 1 year.

Secondary Screening Visit

The purpose of this visit is to confirm study eligibility and collect clinical measurements that can be used to characterize the participant. This visit is limited to a maximum of 5 hours.

Specific Procedures

Participants will be asked to complete a medical history and physical examination to assess neurological complications and medical comorbidities, stroke-specific weakness/balance impairment, cognitive or behavioral issues, and communication issues. Participants may be asked to complete the following:

- NIHSS Cognitive Screen (Only Question 1b and 1c)
- Medical History
- Star Cancellation Test *(Only if study team suspects neglect or hemianopia at any time during the course of the research, the physical therapist may administer the Star Cancellation Test (https://www.strokengine.ca/en/assess/sct/) for neglect or a visual field test (e.g., showing visual stimuli on different sides of the body) for hemianopia.)*
- Assess the strength and mobility of the participant; for example, by using activities that are part of the Fugl-Meyer Assessment of Motor Recovery after Stroke or Functional Gait Assessment. These types of assessments are routine evaluations that physical therapists conduct in typical practice and will provide the research team with a participant's baseline level of disability.
- Assessments to understand participant's physical activity and comfort performing various tasks using questionnaires that ask about the person's confidence in performing various physical activities in different contexts (Activities-Specific Balance Confidence scale) or self-perceived physical activity level (International Physical Activity Questionnaire (IPAQ))
- Overground comfortable walking speed (CWS) and fast walking speed (FWS) assessed using three 10-meter walk tests for each speed
- Overground long-distance walking ability using the 6-minute walk test where the participant will be asked to walk as far as they can as safely as they can in six minutes (exact instructions provided with test in attachment).
- Ask participants to walk at a range of speeds on a treadmill for a brief period (10 minutes or less per speed or incline, with no more than 60 minutes of total walking activity per session) in order to assess their ability to safely do so and to determine safe treadmill speeds for future testing. Walking speeds on the treadmill will be set based on participants' self-selected overground walking speeds. Treadmill speed will be modulated incrementally and investigators, in communication with the participant, will ensure that it is safe to increase speed before doing so. Participants will be harnessed during all treadmill testing to prevent a fall to the ground. Trained study personnel will provide additional guarding to the participant as deemed necessary. Take physiological measurements (e.g., heart rate, blood pressure, respiration rate, or oxygen saturation) before, during, or after these assessments as indicated. Vitals will be monitored by hand (e.g., taking pulse) or

using bodyworn sensors such as a heartrate monitor, electrocardiogram, or pulse oximeter.

- We may also collect Biomechanics data—including kinematics, kinetics, and spatiotemporal parameters—to help further characterize a person's gait. This will not be necessary if the research team feels no additional movement data is needed to characterize an individual's walking pattern (based on data collected with questionnaires, other walking and functional tests, and physical therapist observation done at this visit). Biomechanical data will be collected using commercial equipment common to motion analysis laboratories. These equipment include:
  - An inertial motion capture system. This system gathers information about 3D motion (orientation, acceleration, angular velocity, earth-magnetic field and static pressure) using wireless inertial measurement unit (IMU) sensors that are secured to the body using Velcro straps.
  - An optical motion capture system. This system gathers information about the 3D motion of reflective markers affixed to different segments on the body.
  - An electromyography system. This system measures muscle activation using small sensors affixed over muscle. For accurate EMG sensor reading, the research team may need to shave small areas of the patient's skin where EMG sensors are to be placed (thigh, calf and shin).
  - Force plates. These devices are embedded into the ground and measure ground contact forces by the legs during overground activities such as walking.
  - An instrumented treadmill. This device measures ground contact forces by the legs during treadmill walking. Instrumented handrails allow measurement of support forces exerted during treadmill walking.
  - Metabolic data—e.g., energy expenditure—using a metabolicmeasurement system that measures O_2 consumption and CO_2 production on a breath-by-breath basis through a mask worn over the mouth and nose.
  - Measures may be made during submaximal effort (i.e., walking at comfortable walking speeds). For example, walking economy (i.e., oxygen consumed (ml O_2/kg) per meter ambulated).
- We may also collect information about a person's cardiovascular response to exercise using an electrocardiogram (ECG) if the participant has a history of cardiovascular abnormality (such as an irregular rhythm) that the research team would like to monitor the response of during exercise activities:
  - A trained member of the research team may place electrodes on the chest and/or limbs of the participant.
  - Electrodes are attached to the skin using a medical grade adhesive. Participants may be asked to shave portions areas of the skin where the electrodes will be placed to improve transmission of electrical impulses.
  - A computer will record the electrical impulses of the resting heart rate picked up by the electrodes and display them as waves on a monitor or printed on paper.

Facilities

These visits will occur at the Boston University Neuromotor Recovery Laboratory. Participants will be harnessed at all times during treadmill walking.

Equipment

- Force plates. These devices are embedded into the ground and measure ground contact forces by the legs during over ground activities such as walking.
- An instrumented treadmill. This device measures ground contact forces by the legs during treadmill walking. Instrumented handrails allow measurement of support forces exerted during treadmill walking.
- Blood pressure cuff and Doppler. These systems measure blood pressure using an arm band and sphygmometer, or small ultrasound portable device placed on the participant's skin. For accurate Doppler readings, a small amount of ultrasound gel may need to be put on the patient's skin.
- Heartrate monitor. This device is worn around the wrist or chest to measure heartrate.
- An inertial motion capture system (IMU). This system gathers information about 3D motion (orientation, acceleration, angular velocity, earth-magnetic field and static pressure) using wireless IMU sensors that are secured to the body using Velcro straps.
- An optical motion capture system. This system gathers information about the 3D motion of reflective markers affixed to different segments on the body.
- An electromyography system (EMG). This system measures muscle activation using small sensors affixed over muscle. For accurate EMG sensor reading, the research team may need to shave small areas of the patient's skin where EMG sensors are to be placed (thigh, calf and shin).
- An electrocardiography system (ECG). This system measures cardiac activity using small sensors affixed over the torso. For accurate ECG sensor reading, the research team may need to shave a small area of the patient's skin where the ECG sensors are to be placed.
- Metabolic data—e.g., energy expenditure—using a metabolic measurement system that measures O_2 consumption and CO_2 production on a breath-by-breath basis through a mask worn over the mouth and nose.

Medical Clearance

We will seek medical clearance for qualifying participants who are eligible for the study based on the primary and secondary screenings. This will include both clearance for the entire research study.

Note for all testing visits from this point on: i) we may ask participants to fast (refrain from eating) up to 1 hour before the study visits, but to continue drinking water to ensure they are well hydrated for testing visits; ii) participants will be harnessed during all treadmill walking; iii) photos and videos may also be taken should the participant agree; iv) skin inspections will occur prior to and after each session to check for skin integrity.

Exosuit Fit and Comfort

For participants who have not been fitted previously for an exosuit, an initial fitting day will occur prior to the experimental maximal effort tests. For participants who have already been fitted for an exosuit, a fit and comfort day may still be scheduled to ensure proper fit and provide the participant with a "refresher" on walking with the exosuit if a significant amount of time has passed since their last testing day with the exosuit.

Scheduling

Eligible participants will be scheduled for a fit/comfort study visit that will last up to 4 hours with a limit of 1 hour of walking activities.

Specific Procedures

Study visit procedures will include the following:

- Skin inspection
- Collection of height and weight
- Overground walking assessments (e.g., 6 minute walk test)
- Collection of vitals (heart rate, blood pressure)
- Brief, harnessed treadmill walk
- Fit/Comfort adjustments
- Collection of IMU, motion capture and suit data

The exosuit may be passive (not providing assistance) or active (providing assistance) during the above procedures.

Facilities

Fit/Comfort Day visits will take place at the Neuromotor Recovery Laboratory at Boston University.

Equipment

- Force plates. These devices are embedded into the ground and measure ground contact forces by the legs during over ground activities such as walking.
- An instrumented treadmill. This device measures ground contact forces by the legs during treadmill walking. Instrumented handrails allow measurement of support forces exerted during treadmill walking.
- Blood pressure cuff and Doppler. These systems measure blood pressure using an arm band and sphygmometer, or small ultrasound portable device placed on the participant's skin. For accurate Doppler readings, a small amount of ultrasound gel may need to be put on the patient's skin.
- 3D motion information using inertial measurement units (IMUs): Wireless IMU sensors give us additional information about your movements, such as orientation and acceleration. These sensors are secured to your body using velcro straps.
- Heartrate monitor. This device is worn around the wrist or chest to measure heartrate.

- Exosuit. This system is an unobtrusive and lightweight device that applies assistive joint torques in parallel with the underlying musculature to enhance the residual capacity of the paretic limb. For this study, we will use exosuits developed in collaboration with an industry partner, ReWalk Robotics.

Experiment 1: Maximal Effort Tests (MET)

4 Visit Types:

- MET with an exosuit *and* with intensity modulated using treadmill incline
- MET without an exosuit *and* with intensity modulated using treadmill incline
- MET with an exosuit *and* with intensity modulated using treadmill speed
- MET without an exosuit *and* with intensity modulated using treadmill speed

**Note: During visits that include the exosuit, the exosuit will be active and providing assistance*

Scheduling:

The four METs will be scheduled in randomized order (per participant) and >3 days apart,. Not all participants may complete all four of these visits if (i) it is determined that they are not suitable candidates for this testing or (ii) they decide to withdraw from the study. However, they may be asked to complete all four types of MET visits during this study.

Testing visits will have a limit of 1 hour of walking activities, with walking during a maximal effort test limited to 45 minutes. The total duration of a METs visit will be limited to a maximum 5 hours. Walking during a maximal effort test will be limited to 45 minutes. This testing will occur at the Boston University Neuromotor Recovery Laboratory.

Nature of the MET:

During the MET individuals will walk until peak volitional exertion (i.e., participant requests to stop) or until the participant exhibits any of the symptomatic, clinical, or electrocardiographic criteria in **Table 1.** ***Symptomatic, Clinical, and Electrocardiographic Parameter Guidelines - Outside of Acceptable Range*** of (unless stricter parameters are requested by the participant's physician, in which case the stricter parameters will be used).

Table 1. Symptomatic, Clinical, and Electrocardiographic Parameter Guidelines - Outside of Acceptable Range

Symptomatic Criteria
Shortness of breath
Light-headedness
Confusion

	Severe headache
	Dyspnea
	Moderate to severe angina (> 2 on a 4-point scale)
	Dizziness, syncope
	Wheezing or coughing
Clinical Criteria	
Baseline resting blood pressure (BP) and heart rate (HR) will be obtained and reviewed as follows:	
HR	Resting HR between 50 and 100 bpm, testing will proceed as planned. Resting HR less than 50 bpm or more than 100 bpm, testing will be postponed unless cleared by the participant's physician.
BP	Resting BP less than 150/86 mmHg and more than 90/60 mmHg, testing will proceed as planned. Resting BP outside of this range, testing will be postponed unless cleared by the participant's physician. Participants with a baseline BP greater than 190/110 mmHg will not be eligible for the study.
The following clinical criteria will be used during testing:	
	Drop in systolic blood pressure >10mmHg with an increase in workload
	Systolic blood pressure ≥250 or diastolic blood pressure ≥115mmHg
	Pulse pressure narrowing >10mmHg
Electrocardiographic Criteria	
	Sustained ventricular tachycardia or other arrhythmia (>30 beats)
	New onset of cardiac output altering ventricular dysrhythmias
	ST segment depression of ≥ 2mm or ST elevation ≥ 1 mm

All testing will be conducted by a qualified health professional (e.g., an exercise physiologist, physical therapist, nurse, physician's assistant, or physician) trained to administer exercise tests,

including ECG monitoring. All tests will be conducted with (offsite) oversight provided by a cardiologist consultant (Dr. Ress, MD) who works closely with the PI to ensure that the team is appropriately trained and that the testing procedures and emergency response are appropriate. Dr. Ress will not interact directly with participants, but will be available to consult with the research team as needed. Data shared with Dr. Ress will be de-identified.

Safety Note:

In the event of an abnormal response to exercise testing, or any event that poses a major health risk to the participant, the session will be terminated. Depending on the severity of the situation, study investigators will either refer the participant to the emergency room or contact the participant's healthcare provider to inform him/her of the situation and he/she will determine appropriate medical follow-up.

If an incidental finding is noted during non-screening maximal effort testing, the consulting cardiologist will be sent all test results for interpretation, which will then be sent to the participants' healthcare provider in case it alters their medical care.

Study Visit Procedures:

- The physical therapist will review the participant's medical and physical history obtained during screening with the participant to assess for any changes in since the screening visit.
- A trained and certified phlebotomist (or the equivalent) will collect a 10mL blood sample with or without a catheter. (*This enables measurement of baseline peripheral BDNF levels).* There is an agreement with the GCRU at the BU medical campus to utilize their nurses from blood draws during this study.
- A 2mL saliva sample will also be collected using a commercially available, research grade saliva sample kit for genotyping. Participants will be asked to spit into a test tube with a funnel on top. The funnel will then be discarded, and the test tube will be de-identified and stored at room temperature in a locked cabinet behind a locked door at the Neuromotor Recovery Laboratory at Boston University until it is shipped for processing. The kit manufacturer, will process the de-identified samples and send the results back to the researchers. Following analysis, all saliva samples will be handled via the company's protocol. (*The company will probe for Val66Met SNP, the presence of which modifies peripheral BDNF response to exercise.)*
- A 12-lead resting ECG will be conducted and reviewed for abnormalities by the investigator monitoring the ECG during testing. The participant will be asked to lay supine on a cushioned treatment table, a 12-lead ECG will be attached to the participant, and a 10 second resting ECG will be recorded.
- Resting blood pressure (BP) and heart rate (HR) will be obtained and reviewed
- Optical (Qualisys), inertial (Xsens), and/or EMG (Delsys) movement trackers will be placed on the participant.
- If visit includes MET with exosuit, the study team will then don the exosuit on the participant

Note: ECG monitoring will continue throughout testing procedures, as well as heart rate and blood pressure readings. Participants may also be connected to a metabolic portable unit for indirect calorimetry testing throughout testing procedures.

For Incline-Modulated MET:

- We will don the harness on the participant
- The study team member starts the treadmill at a slow speed and increases to greater than or equal to 85% of participants' fastest walking speed (FWS). The exact speed will be determined by a physical therapist based on evaluations of the participant's baseline level of function and physical safety during walking.
- The participant will walk at this speed at 0% treadmill incline for 2 minutes.
- The study team member will advance to 2-4% treadmill incline for the next 2 minutes.
- The study team member will increase treadmill incline 2-4% every 2 minutes thereafter, while keeping speed constant.
- Testing will continue until peak volitional exertion (i.e., participant requests to stop) or until the participant exhibits any of the symptomatic, clinical, or electrocardiographic criteria in **Table 1. *Symptomatic, Clinical, and Electrocardiographic Parameter Guidelines - Outside of Acceptable Range*** of (unless stricter parameters are requested by the participant's physician, in which case the stricter parameters will be used).
- A trained and certified phlebotomist (or the equivalent) will collect a second 10mL blood sample (with or without a catheter) immediately after walking. *This enables measurement of peripheral BDNF concentration.*

For Speed-modulated MET:

- We will don the harness on the participant.
- The study team member will start the treadmill at a slow speed and increase to the participant's comfortable walking speed (CWS). The exact speed will be determined by a physical therapist based on evaluations of the participant's baseline level of function and physical safety during walking.
- The participant will walk at this speed at 0% treadmill incline for 2 minutes.
- The study team member will advance speed by 5-10% for the next 2 minutes.
- The study team member will increase treadmill speed 5-10% every 2 minutes thereafter while keeping incline constant.
- Testing will continue until peak volitional exertion (i.e., participant requests to stop) or until the participant exhibits any of the symptomatic, clinical, or electrocardiographic criteria in **Table 1. *Symptomatic, Clinical, and Electrocardiographic Parameter Guidelines - Outside of Acceptable Range*** of (unless stricter parameters are requested as by the participant's physician, in which case the stricter parameters will be used).
- A trained and certified phlebotomist (or the equivalent) will collect a second 10mL blood sample (with or without a catheter) immediately after walking. *This enables measurement of peripheral BDNF concentration.*

After Testing:

- BP and HR will be monitored until they return to resting levels.

- A trained and certified phlebotomist (or the equivalent) will collect a third 10mL blood sample 15 minutes after MET test completion. (*This enables measurement of peripheral BDNF concentration (and clearance)).*
- Reflective markers and sensors will be removed.
- If visit includes MET with exosuit, the study team will doff the exosuit.

Note Following the End of the Study Visit

The study team member will follow-up with the participant within 5 days post-session to assess fatigue and/or tolerance to the study procedures. Any finding discovered from this phone call or email will be handled via the Procedures for Adverse Events.

MET Equipment and Facilities

Facilities

MET tests will take place in the Neuromotor Recovery Laboratory at Boston University.

Equipment

- An inertial motion capture system (IMU). This system gathers information about 3D motion (orientation, acceleration, angular velocity, earth-magnetic field and static pressure) using wireless IMU sensors that are secured to the body using Velcro straps.
- An optical motion capture system. This system gathers information about the 3D motion of reflective markers affixed to different segments on the body.
- An electromyography system (EMG). This system measures muscle activation using small sensors affixed over muscle. For accurate EMG sensor reading, the research team may need to shave small areas of the patient's skin where EMG sensors are to be placed (thigh, calf and shin).
- Metabolic portable unit for indirect calorimetry testing. The system measures metabolic data—e.g., energy expenditure—by measuring O_2 consumption and CO_2 production on a breath-by-breath basis through a mask worn over the mouth and nose.
- An electrocardiography system (ECG). This system measures cardiac activity using small sensors affixed over the torso. For accurate ECG sensor reading, the research team may need to shave a small area of the patient's skin where the ECG sensors are to be placed.
- An instrumented treadmill. This device measures ground contact forces by the legs during treadmill walking. Instrumented handrails allow measurement of support forces exerted during treadmill walking.
- Exosuit. This system is an unobtrusive and lightweight device that applies assistive joint torques in parallel with the underlying musculature to enhance the residual capacity of the paretic limb. For this study, we will use exosuits developed in collaboration with an industry partner, ReWalk Robotics.
- Blood pressure cuff and Doppler. These systems measure blood pressure using an arm band and sphygmometer, or small ultrasound portable device placed on the participant's skin. For accurate Doppler readings, a small amount of ultrasound gel may need to be put on the patient's skin.

- Heartrate monitor. This device is worn around the wrist or chest to measure heartrate.

Motor Learning Pilot Study

Following completion of MET tests, we will analyze the data and identify responders and non-responders based on their clinical, biomechanical, and/or physiological response and conduct motor learning experiments across both subsets.

Visit Types

- Exercise with exosuit *followed by* a novel motor learning task
- Exercise without exosuit *followed by* a novel motor learning task

**Note: During visits that include the exosuit, the exosuit will be active and providing assistance*

Scheduling

Up to 20 participants will be invited to return for 4 additional visits. The visit type for each participant will be randomized and scheduled at least 1 week apart. The visits will last up to 4 hours which includes up to 1 hour of walking activities.

Study Visit Procedures

The exercise conducted in this portion of the study will consist of 20-30 minutes of walking at a high intensity (>70% of max HR) on the treadmill, unless that figure exceeds the guidelines set by the participant's physician, in which case the stricter parameters will be used. We may modulate treadmill speed or incline, depending on what the participant can best tolerate.

Following the exercise, the study team will administer a motor learning task, which will involve explicit or implicit learning conducted on the treadmill (e.g., split-belt treadmill walking or walking with biofeedback of gait). This will involve changing the speeds or inclines of the treadmill, or providing auditory and/or visual feedback (e.g., cueing) of walking-related variables.

We will collect the following data at any point during the session:

- Metabolic data
- Vitals (heart rate and blood pressure)
- Overground walking assessments at any point during this pilot study
- Data about human locomotion (IMU, EMG, force plates, suit data, etc.)
- ECG

It is possible a trained and certified team member may collect additional blood and saliva samples before and after the exercise as well; however this will depend on the associations that we find between molecular markers and response to the Maximal Effort Tests (from experiment 1). If strong associations are found, we will collect additional blood and saliva samples during these

Motor Learning visits to further investigate these relationships. We will not collect more than 3 blood samples (10ml each) and 1 saliva sample (2 ml) per study visit.

Note Following the End of the Study Visit

The study team member will follow-up with the participant within 5 days post-session to assess fatigue and/or tolerance to the study procedures.

Facilities

Exercise visits will have a limit of 1 hour of walking activity. Visits will be limited to 4 hours and will be conducted at the Neuromotor Recovery Laboratory at Boston University.

Equipment

- An inertial motion capture system (IMU). This system gathers information about 3D motion (orientation, acceleration, angular velocity, earth-magnetic field and static pressure) using wireless IMU sensors that are secured to the body using Velcro straps.
- An optical motion capture system. This system gathers information about the 3D motion of reflective markers affixed to different segments on the body.
- An electromyography system (EMG). This system measures muscle activation using small sensors affixed over muscle. For accurate EMG sensor reading, the research team may need to shave small areas of the patient's skin where EMG sensors are to be placed (thigh, calf and shin).
- Metabolic portable unit for indirect calorimetry testing. The system measures metabolic data—e.g., energy expenditure—by measuring O_2 consumption and CO_2 production on a breath-by-breath basis through a mask worn over the mouth and nose.
- An electrocardiography system. This system measures cardiac activity using small sensors affixed over the torso. For accurate ECG sensor reading, the research team may need to shave a small area of the patient's skin where the ECG sensors are to be placed.
- Force plates. These devices are embedded into the ground and measure ground contact forces by the legs during over ground activities such as walking.
- An instrumented treadmill. This device measures ground contact forces by the legs during treadmill walking. Instrumented handrails allow measurement of support forces exerted during treadmill walking.
- Exosuit. This system is an unobtrusive and lightweight device that applies assistive joint torques in parallel with the underlying musculature to enhance the residual capacity of the paretic limb. For this study, we will use exosuits developed in collaboration with an industry partner, ReWalk Robotics.
- Heartrate monitor. This device is worn around the wrist or chest to measure heartrate.
- Blood pressure cuff and Doppler. These systems measure blood pressure using an arm band and sphygmometer, or small ultrasound portable device placed on the participant's skin. For accurate Doppler readings, a small amount of ultrasound gel may need to be put on the patient's skin.

<u>Gait Training Evaluations</u>

To further answer Aim #1, we will conduct maximal effort exercise testing both with and without an exosuit before and after a period of gait training that is being conducted as part of a separate (parent) protocol #5220 or #5214. Maximal effort tests will be separated by at least 3 days. This will allow us to collect data regarding the changes in exercise capacity following a period of gait training as well as changes in the individual's physiological and biomechanical responses to exosuit assistance during walking. Blood samples may also be collected during these maximal effort exercise tests. We will ask participants to opt into providing blood samples prior to, immediately post and 15-minutes post maximal effort exercise testing (a total of three, 10mL blood draws per test). In addition, we will collect 1x10mL blood draw pre and post gait training sessions (for a total of two, 10mL blood draws). Data from blood draws will allow us to assess BDNF changes in response to the training visit.

In addition, participants undergoing gait training through a separate parent protocol will not be allowed to participate in additional METs or the Motor Learning Pilot Study visits (as described earlier in this section) until they have completed their parent protocol. This means participants will not be asked to complete secondary screening, medical clearance, or exosuit fit & comfort, maximal effort tests or motor learning pilot study visits. This enrollment option is depicted as "enrollment option #2" in the "EoE_Visit_Chart…" document for this proposal request. If they are interested in enrolling in these other protocol visits after completing the Gait Training Evaluation visits portion, they will be re-consented into the study for these visits specifically.

For Gait Training Evaluation, Maximal Effort Exercise Testing Visit pre- and post- gait training period:

ECG monitoring will continue throughout testing procedures, as well as heart rate and blood pressure readings. Participants will be connected to a metabolic portable unit for indirect calorimetry testing throughout testing procedures.

Study Visit Procedures:

Prior to starting test:

- A trained and certified phlebotomist (or the equivalent) will collect a 10mL blood sample with or without a catheter. (*This enables measurement of baseline peripheral BDNF levels).* There is an agreement with the GCRU at the BU medical campus to utilize their nurses from blood draws during this study.
- A 2mL saliva sample will also be collected using a commercially available, research grade saliva sample kit for genotyping. Participants will be asked to spit into a test tube with a funnel on top. The funnel will then be discarded, and the test tube will be de-identified and stored at room temperature in a locked cabinet behind a locked door at the Neuromotor Recovery Laboratory at Boston University until it is shipped for processing. The kit manufacturer will process the de-identified samples and send the results back to the researchers. Following analysis, all saliva samples will be handled via the company's protocol. (*The company will probe for Val66Met SNP, the presence of which modifies peripheral BDNF response to exercise.)* We may also ask the participant to provide the saliva sample at home, seal in appropriate shipping packaging for biological samples (provided by the manufacturer) and either bring into the laboratory during their testing visit or mail directly to the manufacturer.

- A 12-lead resting ECG will be conducted and reviewed for abnormalities by the investigator monitoring the ECG during testing. The participant will be asked to lay supine on a cushioned treatment table, a 12-lead ECG will be attached to the participant, and a 10 second resting ECG will be recorded.
- Resting blood pressure (BP) and heart rate (HR) will be obtained and reviewed
- Optical (Qualisys), inertial (Xsens), and/or EMG (Delsys) movement trackers will be placed on the participant.
- If the visit includes maximal effort testing with an exosuit, the study team will then don the exosuit on the participant

During test:

- The participant will next move to the treadmill for testing, and we will don the harness on the participant
- The study team member will start the treadmill at a slow speed and increase to greater than or equal to 85% of participants' fastest walking speed (FWS). The exact speed will be determined by a physical therapist based on evaluations of the participant's baseline level of function and physical safety during walking.
- The participant will walk at this speed at 0% treadmill incline for 2 minutes.
- The study team member will advance to 2-4% treadmill incline for the next 2 minutes.
- The study team member will increase treadmill incline 2-4% every 2 minutes thereafter, while keeping speed constant.*
- Testing will continue until peak volitional exertion (i.e., participant requests to stop) or until the participant exhibits any of the symptomatic, clinical, or electrocardiographic criteria in **Table 1. *Symptomatic, Clinical, and Electrocardiographic Parameter Guidelines - Outside of Acceptable Range*** of (unless stricter parameters are requested by the participant's physician, in which case the stricter parameters will be used).
- A trained and certified phlebotomist (or the equivalent) will collect a second 10mL blood sample (with or without a catheter) immediately after walking. *This enables measurement of peripheral BDNF concentration.*

**Given the heterogeneity of neuromotor impairment after stroke, we may modulate either treadmill speed or incline, depending on the participant's abilities, in order to increase the intensity of the exercise test. If speed is modulated during testing, the protocol will be as follows:*

- We will don the harness on the participant.
- The study team member will start the treadmill at a slow speed and increase to the participant's comfortable walking speed (CWS). The exact speed will be determined by a physical therapist based on evaluations of the participant's baseline level of function and physical safety during walking.
- The participant will walk at this speed at 0% treadmill incline for 2 minutes.
- The study team member will advance speed by 5-10% for the next 2 minutes.
- The study team member will increase treadmill speed 5-10% every 2 minutes thereafter while keeping incline constant.
- Testing will continue until peak volitional exertion (i.e., participant requests to stop) or until the participant exhibits any of the symptomatic, clinical, or electrocardiographic criteria in **Table 1. *Symptomatic, Clinical, and Electrocardiographic Parameter Guidelines - Outside of Acceptable Range*** of (unless stricter parameters are requested the participant's physician, in which case the stricter parameters will be used).
- A trained and certified phlebotomist (or the equivalent) will collect a second 10mL blood

sample (with or without a catheter) immediately after walking. *This enables measurement of peripheral BDNF concentration.*

Note: ECG monitoring will continue throughout testing procedures, as well as heart rate and blood pressure readings. Participants may also be connected to a metabolic portable unit for indirect calorimetry testing throughout testing procedures.

Facilities

Gait Training Evaluation maximal effort exercise testing visits pre- and post- gait training will take place in the Neuromotor Recovery Laboratory at Boston University, or in the Motion Analysis Laboratory at Spaulding Rehabilitation Hospital. Exercise visits will have a limit of 1 hour of walking activity. Maximal effort exercise testing visits will be limited to 5 hours.

Equipment

- Metabolic portable unit for indirect calorimetry testing. The system measures metabolic data—e.g., energy expenditure—by measuring O_2 consumption and CO_2 production on a breath-by-breath basis through a mask worn over the mouth and nose.
- An electrocardiography system. This system measures cardiac activity using small sensors affixed over the torso. For accurate ECG sensor reading, the research team may need to shave a small area of the patient's skin where the ECG sensors are to be placed.
- Force plates. These devices are embedded into the ground and measure ground contact forces by the legs during over ground activities such as walking.
- An instrumented treadmill. This device measures ground contact forces by the legs during treadmill walking. Instrumented handrails allow measurement of support forces exerted during treadmill walking.
- Blood pressure cuff and Doppler. These systems measure blood pressure using an arm band and sphygmometer, or small ultrasound portable device placed on the participant's skin. For accurate Doppler readings, a small amount of ultrasound gel may need to be put on the patient's skin.
- Heartrate monitor. This device is worn around the wrist or chest to measure heartrate.

After Gait Training Evaluation, Maximal Effort Exercise Testing Visit pre- and post- gait training period:

- BP and HR will be monitored until they return to resting levels.
    - If vitals do not return to resting levels within a reasonable timeframe, or any major event that poses a health risk to the participant is discovered, the session will be terminated.
    - Depending on the severity of the situation, study investigators will either refer the participant to the emergency room or contact the participant's healthcare provider to inform him/her of the situation and he/she will determine appropriate follow-up.
- Participants will complete a physical activity questionnaire (e.g., the International Physical Activity Questionnaire). If visit time exceeds the 5 hour limit, the participant may also complete this questionnaire over the phone with research personnel or take home to complete on their own.

- A trained and certified phlebotomist (or the equivalent) will collect a third 10mL blood sample 15 minutes after MET test completion. (*This enables measurement of peripheral BDNF concentration (and clearance).*
- Reflective markers and sensors will be removed.
- If visit includes MET with exosuit, the study team will doff the exosuit.

For Gait Training Evaluation blood draws pre and post gait training session:

- A trained and certified phlebotomist (or the equivalent) will collect one 10mL blood sample (with or without a catheter) immediately before the gait training session, and a second 10mL blood draw immediately after the gait training session. *This enables measurement of peripheral BDNF concentration.*
- A 2mL saliva sample will also be collected using a commercially available, research grade saliva sample kit for genotyping. Participants will be asked to spit into a test tube with a funnel on top. Saliva may be collected at home or in-person during the testing visit. The funnel will then be discarded, and the test tube will be de-identified and stored at room temperature in a locked cabinet behind a locked door at the Neuromotor Recovery Laboratory at Boston University or at Spaulding Rehabilitation Hospital until it is shipped for processing. The kit manufacturer, will process the de-identified samples and send the results back to the researchers. Following analysis, all saliva samples will be handled via the company's protocol. (*The company will probe for Val66Met SNP, the presence of which modifies peripheral BDNF response to exercise.)*

Facilities

Gait Training Evaluation blood draws pre and post gait training session will take place in the Neuromotor Recovery Laboratory at Boston University, or in the Motion Analysis Laboratory at Spaulding Rehabilitation Hospital.

Additional Procedures for Individuals with Diabetes for All Study Visits–

- If you have insulin dependent diabetes, you will be required to bring your own glucometer and test your blood sugar level prior to the session, at the completion of each session, and at any time you experience symptoms. If blood sugar levels are less than 60 mg/dL or greater than 300 mg/dL, you will not participate in the study that day. You will be provided with juice and crackers, or you may provide yourself with insulin per your typical routine. We will contact your primary healthcare provider to inform them of the blood sugar levels and he/she will determine appropriate medical follow-up.
- If you have non-insulin dependent diabetes and do not own a glucometer or do not regularly take glucometer readings at home, you will not be required to test your blood sugar levels; however, you may be asked to stop during a training if you show any of the following symptoms: confusion, excessive perspiration, difficulty speaking, excessive hunger or thirst, excessive fatigue, dry mouth, dizziness/light-headedness, headache, shakiness. If a negative response occurs, the testing will be stopped and appropriate clinical care will be given during the episode. We will contact your primary healthcare provider to inform them of the episode.

- If you regularly use a glucometer, but do not bring it with you, testing will be rescheduled to a different day and you will be reminded to bring your glucometer

HUMAN BIOLOGICS ANALYSIS PROCEDURES

I. Blood Sample Packaging and Transportation
II. Saliva Sample Packaging and Transportation
III. Blood Sample Storage
IV. Saliva Sample Storage
V. Blood Sample Analysis
VI. Saliva Sample Analysis

Blood Sample Packaging and Transportation

A member of the research team will transport the blood samples from Boston University to the Stroke Biological Recovery Laboratory at Spaulding Rehabilitation Hospital. These individuals will have undergone transportation training through the Boston University Environmental Health and Safety (EHS) office, which will be available with the regulatory documents for this study.

Sample packaging and transportation outlined below was developed in accordance with the US Department of Transportation Shipping Regulations for Clinical Specimens. The below procedures will only be modified in accordance with changes to the regulations.

Sample Packaging

All samples will be triple packaged and may include ice –

1.) Each sample will be contained in a primary specimen container.
2.) Specimen containers will then be put in a bag. *If transporting multiple samples, each primary container will be wrapped in paper towels to prevent them from hitting each other.*
3.) The secondary container will be put in the outer transport container (which contains a biohazard sticker and a Bill of Lading).

The Bill of Lading is a list of exactly what is being transported. It contains –

- Date of transportation
- The shipper's name, institution, and phone number
- The recipient's name, institution, and phone number

The Bill of Lading is valid for one trip only. All Bills of Lading will be kept with the study documents.

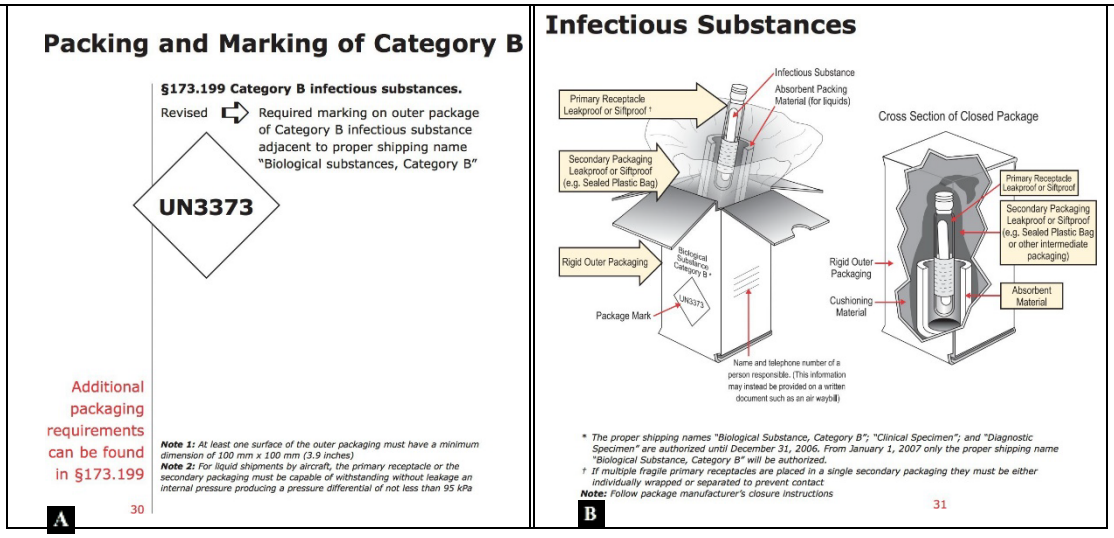


Figure 1. §173.199 Category B infectious substances packaging. Panel A shows required markings on outer package. Panel B illustrates primary, secondary, and outer packaging. Adapted from *U.S. Department of Transportation* ***Pipeline and Hazardous Materials Safety Administration.*** **(2006).** Retrieved July 25, 2018, from ***https://hazmatonline.phmsa.dot.gov/services/publication_documents/Transporting%20Infectious%20Substances%20Safely.pdf***

Transportation

All samples will be transported to the Stroke Biological Recovery Laboratory, prior to which they will be held in a small test tube rack or on ice. If the samples are temporarily stored at Boston University in a refrigerator, they will be stored in a fridge that is designated for clinical samples only, which will be labeled with a biohazard sticker on the outside fridge door.

- Samples will not be transported via public transportation (e.g., MBTA).
- A study team member with U.S. Department of Transportation Hazardous Material Shipping Training (USDOT Training) may drive the samples from Boston University to Spaulding, as long as no one else is in the car (unless passengers have USDOT Training as well).
- A study team member with USDOT Training may take a cab only if the cab driver also has USDOT Training. In order to utilize this method, the study team will need to obtain some form of correspondence verifying that the specific cab driver has this training.

Saliva Sample Transportation

Saliva samples will be shipped using regular mailing service according to the manufacturers recommendation, which also complies with International Air Transport Association (IATA) regulations for samples not expected to be pathogenic (since some "ground" mail may include

flight components). We will use the shipping materials provided by the manufacturer as listed below.

- Capped collection kit vial (with or without secondary rigid plastic container).
- A liquid-tight bag with biohazard logo to hold the capped collection kit vial.
- Absorbent material in the liquid-tight bag sufficient to soak up at least 4 mL of liquid.
- An outer mailing envelope labeled with the words "Exempt Human Specimen"

Blood Sample Storage

Dr. Qing Mei Wang, MD, PhD, the director of the Stroke Biological Recovery Lab at Spaulding Rehabilitation Hospital is providing laboratory space for blood storage, processing, and analysis.

Blood samples will be labeled with the participant's unique ID number and may be kept in a -80C freezer at Spaulding and will be discarded once all participant samples are analyzed.

The samples will not be used for any other purpose other than that which is described below under ***V. Blood Sample Analysis***.

Saliva Sample Storage

Saliva sample test tubes will be de-identified (labeled with participant codes) and stored at room temperature in a locked cabinet behind a locked door at the Neuromotor Recovery Laboratory at Boston University until shipped to the manufacturer (i.e., DNA Genotek Inc. or a manufacturer with similar capabilities).

Blood Sample Analysis

Boston University PhD student, Anna Roto, will be analyzing blood samples in the Stroke Biological Recovery Lab under the supervision of the director of the lab, Dr. Qing Mei Wang, MD PhD.

Specifically, an ELISA assay will be conducted to detect BDNF and a colorimetric assay for lactate concentration analysis. Lactate concentrations will be measured because this is a biomarker of exercise intensity.

Saliva Sample Analysis

The saliva kit manufacturer (i.e., DNA Genotek, Inc. or a manufacturer with similar capabilities), will process saliva samples according to their purification and quantification protocol. The company will probe for Val66Met SNP, the presence of which modifies peripheral BDNF response to exercise. Following analysis, all saliva samples will be handled via the company's protocol.

PROCEDURES FOR ADVERSE EVENTS

(1) Procedures for significant events (vitals that do not return to baseline within a reasonable timeframe, or other incident deemed major in significance by the clinical team member):

- ***Immediate Action -*** If the significant adverse event requires immediate medical attention, the participant will be referred to the emergency room facilities at one of the hospitals neighboring Boston University/in the Boston area.

  OR

  If the significant event does not require immediate medical attention, the IRB-approved physical therapist will contact (call) the participant's treating physician to inform him/her of the measurements and he/she will determine medical follow-up. If the clinical team member does not hear back from the physician or physician's office (within a reasonable timeframe) after attempting to contact them, he/she will make the decision about the immediate medical management of the participant at the time.
- ***Follow-Up Plan for Significant Events Requiring Subsequent Medical Clearance as Determined by the IRB-Approved Physical Therapist –*** A medical findings letter may be sent to the participant's treating physician to inform him/her of the measurements *(See Medical Findings Letter)*. If subsequent medical clearance is determined necessary at the discretion of the clinical research team, a second letter may be sent to the healthcare provider to seek medical clearance prior to proceeding with any additional sessions *(See Medical Findings Follow-Up Letter)*.
  - We will call the healthcare provider's office prior to sending a medical clearance letter to let them know to expect it.
  - We will then follow up with two phone calls, approximately 5 days apart to confirm it was received and to request a response from the healthcare provider.
  - We will ask the healthcare provider to email/fax the completed response to us.
    - The participant's physician may indicate continued participation is acceptable, continued participation with suggested physiological parameters, or withdrawal of the participant from the study.
    - The participant's physician will be responsible for determining any appropriate medical follow-up that may be needed.

  Note: If we do not receive a response from the physician after the two follow-up phone calls, we will ask the participant to follow up directly with their physician's office to encourage them to respond. If the physician denies clearance the participant will be withdrawn from the study. If the physician is unresponsive, medical clearance may be sought from one of the participants' other treating physicians. If that physician does not approve participation, the participant will be excluded and we will not ask for another opinion from another physician. This latter option is designed so participants will not be excluded solely because their providers are unresponsive.

(2) Procedures for less significant/minor events (vitals that return to baseline within a reasonable timeframe, and other incident deemed minor in significance by clinical team):

- ***Immediate Action -*** The IRB-approved physical therapist will make the decision about the management of the participant at the time and will use his/her clinical judgement to determine whether or not it is safe to proceed with the session, modify procedures for the remainder of the session, or terminate the session.

- ***Follow-Up Plan for Less Significant Events Not Requiring Subsequent Medical Clearance as Determined by the IRB-Approved Physical Therapist -*** At the discretion of the physical therapist, a medical findings letter may be sent to the treating physician if the physical therapist feels it is necessary to inform him/her of the measurements. In this case, we will proceed with additional testing visits. If a medical findings letter has been sent, and subsequent medical clearance is not determined necessary at the discretion of the research team, a second letter may be sent to the healthcare provider to inform him/her of the plan to continue scheduling testing sessions with the participant. The participant's physician will be given the opportunity to provide additional monitoring guidelines for this participant or to request the participant's withdrawal from the study, however this mustbe received within one week of the post-marked date of the letter.

SECTION M: RISKS

Describe any expected risks to subjects. Consider physical, psychological, social, political, legal, economic, or other risks that are related to the study.

Possible Risks:

- Swelling, numbness, tingling (suit fit)
- Blisters, rubbing, chaffing
- Fatigue
- Nausea
- Shortness of breath
- Muscle or joint soreness/muscle cramps
- Loss of balance or fall
- Skin redness/inflammation/chafing/hair pulling (from sensor tape)
- Bleeding, small cuts, abrasions, razor burn
- Chest pain
- Discomfort
- Unintentional distraction

Swelling, numbness, tingling; Blisters, rubbing chafing – We do not anticipate fit and comfort tests to be physically strenuous to the participant. As with any assistive device, there is a length of time required for the user to feel comfortable wearing it. Participants will be given ample amount of time to feel comfortable whilst wearing the suit.

The participant may experience minor redness, chafing, blistering, swelling, numbness or tingling due to the tightness of the suit. These are only temporary effects and should disappear over time. Blisters on feet may also result due to rubbing/movement of feet in shoes. Proper fit of shoes will be enforced by the study physical therapist(s), and inspection of feet prior to and after training sessions will be performed. The physical therapist(s) will also inspect the skin on the participant's shank and feet prior to and after each study visit.

Fatigue; Nausea; Shortness of breath; Muscle or joint soreness/muscle cramps; Chest pain; Discomfort – Usability tests are anticipated to be physically strenuous. The participant may become fatigued, or experience joint soreness in their hip, knee, ankle or foot.

As with any exercise, there is the possibility that abnormal responses could occur. These include nausea, shortness of breath, fatigue, muscle cramps or muscle soreness (lasting into subsequent days after testing), chest pain or discomfort. To mitigate these risks, the study physical therapist will monitor vital signs at each study visit and check for symptoms of distress. The physical therapist will use his/her discretion to determine whether it is safe to continue the session, modify the study procedures, or terminate a session prematurely.

Loss of balance or fall – Participants will be harnessed during all treadmill walking. If a harness/strap system is not used during overground walking, there is a risk of falling to participants. The physical therapist will be present at participant's study visits to provide additional support and/or guarding during these circumstances. Unharnessed overground walking would only occur with these participants if the physical therapist has determined that it is safe to do so.

Participants who typically wear an ankle brace may not be able to wear it during testing or training. When walking without the brace, the foot and ankle may not be as stable and can have a risk of twisting while walking. The physical therapist will use clinical judgment to ensure that participants are safe to walk without a brace.

Skin redness/inflammation/chafing/hair pulling (from sensor tape) **–** The double-sided medical grade tape used to place the motion capture markers and EMG sensors on the participant may cause some slight skin redness when taken off. This is a normal reaction and will disappear with time. Hair may also be pulled by the sensor tape. If of concern, the study team will remove tape with hypoallergenic wipes to mitigate this risk.

Bleeding, small cuts, abrasions, razor burn – Participants may be asked to shave small areas of their skin (thigh, calf, shin) where EMG sensors are to be placed. A research team member may assist with shaving to further minimize any effects of the razor on the skin (e.g., bleeding, cuts, razor burn). Some sensors or devices have edges that may irritate or cause abrasions on skin. Study team members may assist with donning of these devices or sensors to prevent any abrasions or discomfort.

Unintentional distraction – Additionally, with the potential use of cueing during the novel motor learning task there may be a risk of unintentional distraction or dizziness as participants focus on the cues while walking.

Less Likely Risks:

- Muscle strain/tear
- Injury due to fall (ankle sprain, twisted knee, etc.)
- Abnormal physiological response to physical activity
- Irregular heart rate
- Fainting

- Rash/itchiness (from sensor tape)
- Pinching/hair pulling (from fans)
- Bruising and bleeding

Muscle strain/tear; Injury due to fall –METs are anticipated to be physically strenuous. Injuries such as muscle strains and tears are possible. Injuries due to falling are also possible.

Abnormal physiological response; Irregular heart rate; Fainting – As with any exercise, there is the possibility that abnormal responses could occur. These include unexpected changes in blood pressure, irregular heart rate, fainting, or joint injury. To mitigate these risks and ensure that participants are safe to participate in study procedures, we will obtain medical clearance from their physician prior to enrollment in the study. Additionally, the study physical therapist will monitor vital signs at each study visit and check for symptoms of distress. The physical therapist will use his/her discretion to determine whether it is safe to continue the session, modify the study procedures, or terminate a session prematurely.

Rash/itchiness (from sensor tape) – The double-sided medical grade tape used to place the motion capture markers and EMG sensors on the participant may cause some slight skin redness when taken off. This is a normal reaction and will disappear with time. Hair may also be pulled by the sensor tape. If of concern, the study team will remove tape with hypoallergenic wipes to mitigate this risk.

Pinching/hair pulling (from fans) – Some of our systems may use fans to prevent them from overheating. These fans are similar to what you would find in a desktop computer. A protective grill prevents objects from contacting the fan blades, but it is possible that long hair could become entangled in the fan or that someone could fit a small finger through the grill. The fans are low powered and should not cause serious injury, and will be monitored by research staff to ensure that their placement on the wearer minimizes the risk of coming into contact with long hair or other body parts.

Bruising and bleeding – Participants who are taking anticoagulants may be at increased risk for bruising and bleeding due to a fall.

Rare Risks:

- Heart problems
- Hospitalization
- Burn
- Shock
- Anxiety
- Heart attack
- Death

Heart problems; Hospitalization; Heart attack; Death – Rare risks associated with intense exercise could include heart problems, hospitalization, heart attack or death. There is also a risk of pulmonary embolism in participants with known history of Deep Vein Thrombosis. To mitigate these risks and ensure participants are good candidates, we will obtain medical

clearance from their healthcare provider prior to enrollment in the study. Additionally, the study physical therapist will monitor vital signs at each study visit and check for symptoms of distress. The physical therapist will use his/her discretion to determine whether it is safe to continue the session, modify the study procedures, or terminate a session prematurely.

Burn; Shock – As with any electrical device, there is a minimal risk of electric shock or burn. There has been a previous reported incident of a minor burn with the wired EMG system we may use in this study. Although the likelihood of a recurrence is rare, we have periodic equipment and data checks in place to minimize this risk. All wires will be coated, minimizing any risk of electrical shock. As an additional safety measure, individual electronic devices/sensors/modules will be safety certified by staff engineers, being put through a safety-checklist before being applied and worn by a human. The motor controllers have built-in safety measures to detect shorted or unconnected phases and cut power to the system. We have also designed an emergency stop switch that can be used by the operator to instantly cut the power to the motor phases in case of unexpected error.

Burn – Some of our systems are powered by batteries which, if shorted, could have a risk of fire. In order to mitigate this risk, the batteries are protected by a fuse to minimize the effects of a short. The battery connector geometry is designed so that the batteries can only be connected in the correct orientation, and battery charging and setup will only be performed by trained research staff.

It is also possible, but unlikely, that the external surfaces of the body-worn actuator could overheat and cause a burn in the event of accidental contact with the wearer. The body-worn actuator has built-in safety measures to detect and prevent incidents of overheating, and the actuator is separated from the wearer by an insulating layer to minimize any accidental contact.

Anxiety – There also is a potential risk for participants who become easily anxious from the metabolic measurement system mask. The mask covers participant's mouth and nose, but can be easily removed if the participant seems agitated or anxious. Similar risks exist with the suit and study procedures; however, these are even less likely than those from the mask and will be monitored in a similar manner.

Risks Associated with Blood Draws (with or without a catheter):
A trained and certified phlebotomist (or the equivalent) will conduct blood draws. It is possible that the trained and certified study team member may use a catheter to draw blood to minimize the number of insertions. Additionally, the professional drawing blood will compress the draw site as needed (up to several minutes) to reduce the risk of excessive bleeding, and participants will be monitored after the blood draw to ensure they are well enough to leave on their own. The below risks are associated with blood draws and use of a catheter.

- Pain/Discomfort at the site of the blood draw
- Bruising
- Redness/Swelling
- Anxiety/Stress
- Bleeding

- Lightheadedness, fainting, nausea
- Blood accumulation under the skin (bruising)
- Vein damage
- Phlebitis
- In very rare circumstances, infection at the site of the blood draw
- In very rare circumstances, venous air embolism

Phlebitis, which is inflammation of a vein caused by trauma to a vein or in this case inception of a catheter. Participants may experience redness, tenderness, and swelling close to the site of the catheter; pain, burning, or throbbing that spans the length of the vein; or feeling as though the vein is warm, hard or cord-like.

Venous air embolism occurs when air bubbles enter a blood vessel. Most air emboli that enter the veins stop at the lungs, so it is rare for an air embolism to show any symptoms.

Risks of Completing Tasks
Participants may get tired. They are able to rest at any time.

Describe the plan to minimize risks. Include in the description the availability of any medical or psychological resources.

The PI and co-investigators have extensive experience with clinical research involving individuals poststroke. Many of the investigators are licensed physical therapists and most study personnel and students have training in CPR and first aid. All of the aforementioned risks will also be mitigated through the following:

- Potential participants will be provided with the consent form and be provided ample time to read it and ask questions. The research team will address any concerns. Participants will be told that participation in the study is completely voluntary and they have the right to withdraw from the study at any time.
- Adequate rest periods and water will be provided to optimize comfort and reduce fatigue.
- Total walking time per session will be limited to one hour.
- Trained investigators will monitor vital signs and check for symptoms of distress at each study visit. Any findings out of the ordinary will be reported to the participant's primary healthcare provider.
- A physical therapist will determine the clinical need to use overhead harnessing based on the participant's gait pattern and fall risk. Treadmill and over-ground walking tests will be completed with overhead harnessing as needed to prevent a fall. In situations where harnessing is not possible (i.e., transitioning between activities), testing activities occurring outside of the lab in the hallway, or when harnessing is not clinically necessary, an investigator will guard the participant, using a gait belt if indicated.
- Trained study investigators will ensure that participants are safe to walk without a brace.

- For each participant, we will obtain medical clearance from their primary healthcare provider prior to begin study procedures (following the secondary screen).
- A research team member will offer to assist with shaving, if needed, to further minimize any effects of the razor on the skin (e.g., bleeding, cuts, razor burn).
- All participants are free to end testing or procedures that cause anxiety or discomfort at any time, this will not affect any remuneration or transportation they are entitled to

SECTION N: BENEFITS

Describe the potential benefits to subjects related to the study. State if there are no direct benefits. NOTE: Compensation and/or course credit are not considered benefits.
There are no direct benefits to participants as a result of participating in this research.
Describe the potential benefits to society and/or others related to the study
This project will facilitate the development and clinical translation of targeted gait interventions that can improve poststroke walking ability through specific action on the impairments most likely to be limiting mobility and participation after stroke, including the development of new technology that extends the abilities of clinicians.

SECTION O: COSTS/PAYMENTS

YES*	NO	
☒	☐	Are there any costs to subjects as a result of participating in this study? **If YES**, provide a description of the costs: Participants will be responsible for any up front costs related to traveling to Boston University, however they will be reimbursed up to $25 (see below).
☒	☐	Will subjects be compensated for participating in the study? Compensation may include cash, checks, gift cards, lotteries, course credit, etc. Payments should be prorated to compensate subjects for time and procedures completed **If YES**, provide a description of the compensation: Participants will receive up to $25 per visit to reimburse expenses incurred as a result of traveling to Boston University for this research. Additionally, parking will be covered by the study.
☐	☒	Will identifiable information be sent to Central University departments (e.g. Accounts Payable, Post Award Financial Operations, etc.) for payment purposes? **If YES**, this information must be disclosed in the consent form.

SECTION P: CONFIDENTIALITY OF DATA

Describe how data will be stored (e.g. paper, electronic database, etc.)
Research participants will be informed that all data collected for study purposes will be held in strict confidence and used for research purposes only. Records may be paper or electronic. ***Paper Documents –*** Screening information (including questionnaires, screening and consent forms, HIPAA Authorizations, and medical clearance letters) will be kept in paper format and stored in a locked file cabinet that only the research team has access to. Participant files may also be scanned and stored on a secure, password-protected server authorized to store restricted data by BU IS&T Information Security team on the BU network, with access provided only to the PI and key personnel. ***De-Identified Participant ID Number –*** Data collected during this research will be labeled using a de-identified participant ID number. ***Blood/Saliva -*** All blood and saliva samples will be labeled with the de-identified alphanumeric code and no other identifiers. ***Research Data –*** Data will be de-identified and stored on a secure, password-protected server with access limited to the research team. Videos and photos and other de-identified data (for example, motion capture data) may be transferred as a local copy to password-protected personal computers for processing or to prepare media material for publications, presentations or training purposes. ***Photos/Videos –*** Participants will be asked to confirm their comfort with having photos/videos taken during the testing (check off box in consent form) and will be told about our procedures to de-identify and retain the data, and how they may request for it to be removed from our storage. • Video and photographic data that is taken will be shared within the research team to assist with device design, development and characterization. • Data, images, and recordings may also be used with our collaborators, or in publications, presentations, or for teaching and training purposes. If data, videos, or photos were used in this manner, none of the participants' identifiers would be included with them. • Video and photo data will not contain any participant names, and will be stored on the BU Network and password protected server with access limited to the research team.

YES*	**NO**	
☒	☐	Will you collect identifiable information? (e.g. names, social security numbers, addresses, telephone numbers, etc.). **If YES**, complete the box below.
Describe the coding system that will be used to protect the information including who will have access to the code. Coding systems are used to: 1) protect the confidentiality of the research data and 2) allow the investigator to link subjects to their responses. Each subject is assigned a unique study ID at the beginning of the study. A separate document (key) should be maintained that links the names of the subjects to the study ID numbers.		

To ensure confidentiality of all data collected, each subject will be assigned a unique alphanumeric code. Only the PI and designated research personnel associated with the project will have access to the master-code with the corresponding identifiers. The master-code will be housed on a password protected network drive.

YES*	NO	
☒	☐	Will you share data with others outside of the study? **If YES**, complete the box below.

Describe how data will be transferred and how confidentiality will be maintained (e.g. identifying information will not be sent outside, etc.):

It is possible a participant's identifiable data may be shared between collaborating institutions including Spaulding Rehabilitation Hospital, when/if participants are interested in multiple research studies in the area, possibly at the same time. This may include, but is not limited to, screening forms, medical history, and study results. This will be done in order to better meet the needs of the participant and synchronize enrollment across multiple studies for which they are interested in participating. Any identifiable data shared with collaborating institutions will be transferred through secure email or server, and will be stored on a secure server at the collaborating institution. Any data provided to Boston University will be treated as identifiable data and will be stored appropriately. The request to share information beyond the study team will be an option to participants on the Informed Consent form. Participants will be able to take part in the study even if they do not want their information shared beyond the study. Information will not be shared, and participants will not be contacted for additional studies, unless they have given their permission via the consent form. Only de-identified data will be shared with researchers at Harvard University.

Describe how you will maintain the confidentiality of the data (e.g. locked cabinet, password-protected files, encryption, etc.). Note: Confidentiality refers to the researcher's agreement with the participant about how the subject's identifiable private information will be handled, managed, and disseminated. For further assistance and/or access to resources regarding information security, please refer to the BU Information Security website**.**

Only the PI and a few designated research personnel will have access to identifiable research data. The PI and all study personnel (listed in section E) will have access to all coded data housed on a password-protected secured network drive. Paper forms will be stored in a locked filing cabinet in a locked office. No names or identifiers of subjects will be contained on paper forms or entered into a database. No identifiable data will be shared with non-study personnel including students, professional colleagues, outside institutions or study sponsors.
No identifiable data will be used in scholarly presentations, in future research projects and in publications.

Per Boston University (BU) Record Retention Policy, records concerning human subjects must be retained for 7 years. As the investigator, you must also adhere to all applicable requirements as defined by regulatory agencies (e.g. FDA, etc.) or Sponsors.

SECTION Q: CERTIFICATE OF CONFIDENTIALITY

In 2017 the NIH updated its policy for issuing **Certificates of Confidentiality**. Under the policy, all **eligible** research studies funded by the NIH are automatically issued a certificate of confidentiality. Investigators whose research is not funded or supported by the NIH may request and obtain from the NIH a Certificate of Confidentiality. Investigators who request and receive Certificates must follow the NIH and PHS policies governing such certifications.

YES	NO	
☐	☒	Is your research funded by the NIH and eligible for a Certificate of Confidentiality?
☐	☒	If your research is not funded by the NIH, will you be applying for a Certificate of Confidentiality?

SECTION R: PRIVACY

Describe how you will protect the privacy of subjects (e.g. where will consent procedures take place, if interviews or other interventions, where will these procedures take place)

Privacy of participants will be protected by conducting all in-person interactions in a semi-private or private space within the Neuromotor Recovery Laboratory located at the Track and Tennis Center. No personally identifiable information will be discussed in common areas.

Photos/Videos **–** Participants will be asked to confirm their comfort with having photo/video taken during the testing (check off box in consent form).

- All video and photographic data that is taken will not contain any participant names and will be stored on a password protected server with access limited to the research team.

Personal Health Information **–** Any medical records obtained during the course of the study will be de-identified and labeled only with a letter/number combination for each participant. The HIPAA authorization for disclosure of protected health information will be kept with other participant (de-identified and identifiable) information in a locked file cabinet accessible only to pertinent research team members.

SECTION S: MONITORING STUDY DATA

How will data be monitored?

Note: The Data and Safety Monitoring Plan should be tailored to the nature, size, and complexity of the research protocol, the expected risks of the research, and the type of subject population being studied.

☒	Principal Investigator
☐	Monitor/Monitoring Group

☐	Data and Safety Monitoring Board (DSMB) Note: The DSMB Charter must be submitted with this Application. For more information regarding a DSMB, please refer to the NIH website.

Describe the plan for monitoring study data. This should include a description of how data will be collected and analyzed as the project progresses to assure the appropriateness of the research, its design, and subject protections.

Data will be de-identified (using participant assigned alphanumeric code) and collected according to NRL data collection SOPs. This de-identified data will be processed and analyzed by the PI and research team (Section E). Data will be analyzed using as soon as possible after collection to assure the appropriateness of the research design and subject protections.

PROCEDURES FOR ADVERSE EVENTS

(1) Procedures for significant events (vitals that do not return to baseline within a reasonable timeframe, or other incident deemed major in significance by the clinical team member):

- ***Immediate Action -*** If the significant adverse event requires immediate medical attention, the participant will be referred to the emergency room facilities at one of the hospitals neighboring Boston University/in the Boston area.

  OR

  If the significant event does not require immediate medical attention, the IRB-approved physical therapist will contact (call) the participant's treating physician to inform him/her of the measurements and he/she will determine medical follow-up. If the clinical team member does not hear back from the physician or physician's office (within a reasonable timeframe) after attempting to contact them, he/she will make the decision about the immediate medical management of the participant at the time.

- ***Follow-Up Plan for Significant Events Requiring Subsequent Medical Clearance as Determined by the IRB-Approved Physical Therapist –*** A medical findings letter may be sent to the participant's treating physician to inform him/her of the measurements *(See Medical Findings Letter)*. If subsequent medical clearance is determined necessary at the discretion of the clinical research team, a second letter may be sent to the healthcare provider to seek medical clearance prior to proceeding with any additional sessions *(See Medical Findings Follow-Up Letter)*.
  - We will call the healthcare provider's office prior to sending a medical clearance letter to let them know to expect it.
  - We will then follow up with two phone calls, approximately 5 days apart to confirm it was received and to request a response from the healthcare provider.

- We will ask the healthcare provider to email/fax the completed response to us.
    - The participant's physician may indicate continued participation is acceptable, continued participation with suggested physiological parameters, or withdrawal of the participant from the study.
    - The participant's physician will be responsible for determining any appropriate medical follow-up that may be needed.

***Note:** If we do not receive a response from the physician after the two follow-up phone calls, we will ask the participant to follow up directly with their physician's office to encourage them to respond. If the physician denies clearance the participant will be withdrawn from the study. If the physician is unresponsive, medical clearance may be sought from one of the participants' other treating physicians. If that physiciandoes not approve participation, the participant will be excluded and we will not ask foranother opinion from another physician. This latter option is designed so participants will not be excluded solely because their providers are unresponsive.

(2) Procedures for less significant/minor events (vitals that return to baseline within a reasonable timeframe, and other incident deemed minor in significance by clinical team):

- ***Immediate Action -*** The IRB-approved physical therapist will make the decision about the management of the participant at the time and will use his/her clinical judgement to determine whether or not it is safe to proceed with the session, modify procedures for the remainder of the session, or terminate the session.

Follow-Up Plan for Less Significant Events Not Requiring Subsequent Medical Clearance as Determined by the IRB-Approved Physical Therapist - At the discretion of the physical therapist, a medical findings letter may be sent to the treating physician if the physical therapist feels it is necessary to inform him/her of the measurements. In this case, we will proceed with additional testing visits. If a medical findings letter has been sent, and subsequent medical clearance is not determined necessary at the discretion of the research team, a second letter may be sent to the healthcare provider to inform him/her of the plan to continue scheduling testing sessions with the participant. The participant's physician will be given the opportunity to provide additional monitoring guidelines for this participant or to request the participant's withdrawal from the study, however this must be received within one week of the post-marked date of the letter.

SECTION T: HIPAA
Health Insurance Portability and Accountability Act

YES*	NO	

☐	☒	Is this research being conducted in a covered entity?
		The following BU CRC Departments are considered covered entities:
		• Sargent College Rehabilitation Services
		  ○ Physical Therapy Center at the Ryan Center for Sports Medicine and Rehabilitation
		  ○ Sargent Choice Nutrition Center
		• The Danielsen Institute
		• Boston University Health Plan
		*If YES, contact the IRB office for assistance.

SECTION U: FAMILY EDUCATIONAL RIGHTS AND PRIVACY ACT (FERPA)

: FERPA is the federal law that protects the privacy of student education records. Research funded by the Department of Education or research conducted in educational institutions that receive funds from the Department of Education (for research or other purposes) must comply with FERPA.

YES*	NO	
☐	☒	Does this study involve collection of information from student school/university records? *If YES, refer to the following websites for guidance on FERPA: • http://www.bu.edu/researchsupport/compliance/human-subjects/ • http://www.bu.edu/reg/general-information/ferpa/ • http://www2.ed.gov/policy/gen/guid/fpco/ferpa/index.html **If FERPA applies, you must complete the box below:**
In accordance with FERPA, written consent must be obtained to access student records. The consent must: • Specify the records that may be disclosed • State the purpose of the disclosure • Identify the person or class of parties to whom the disclosure can be made		
☐ YES **(REQUIRED)**		I confirm that I will comply with the FERPA policy that is in place at the educational institution where I am conducting my research. This includes, if applicable, the requirements for written agreement when requesting a waiver of consent for personally identifiable information. **If an agreement is required, this agreement must be submitted to the IRB.**

SECTION V: PROTECTION OF PUPIL RIGHTS AMENDMENT (PPRA):

PPRA is a federal law that affords certain rights to parents of minor students with regard to surveys that ask questions of a personal nature. Research funded by the Department of Education or research conducted in educational institutions that receive funds (for research or other purposes) from the Department of Education must comply with the PPRA.

YES*	NO	
☐	☒	Does PPRA apply to this study? If YES, refer to the following websites for guidance: • http://www2.ed.gov/policy/gen/guid/fpco/ppra/index.html • http://www.bu.edu/researchsupport/compliance/human-subjects/

		If PPRA applies, you must complete the box below:
In accordance with PPRA, written parental consent must be obtained prior to subjects participation in the study.		
☐ YES **(REQUIRED)**		I confirm that I will comply with the PPRA policy that is in place at the educational institution where I am conducting my research.

SECTION W: CLINICAL TRIALS REGISTRATION:

The Food Drug and Administration Amendments Act (known as FDAAA 801) requires that "applicable clinical trials" be registered and have results reported on clinicaltrials.gov. In addition, the International Committee of Medical Journal Editors (ICJME) and the National Institutes of Health (NIH) also have requirements for registration. Please see box below to determine if your study requires registration in accordance with either FDAAA 801, ICJME, or NIH.

YES	NO	FDAAA 801 Requirements
☐	☒	Does your study meet the definition of an applicable clinical trial (ACT) and require registration **AND** results submission in accordance with FDAAA 801? ACTs include: • Trials of drugs and biologics: Controlled clinical investigations, other than phase 1 clinical investigations, of drugs or biological products subject to Food and Drug Administration (FDA) regulation • Trials of devices (see note): 1) Controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and 2) pediatric post-market surveillance required by FDA **Note:** If your study meets the requirement for registration and reporting, you must submit the National Clinical Trial (NCT) Identifier # to the IRB prior to IRB approval**.** NCT #:
YES	**NO**	**ICMJE Requirements**
☐	☐	Does your study meet the definition of a clinical trial and require registration in accordance with ICMJE? **Note:** If your study meets the requirement for registration, you must submit the National Clinical Trial (NCT) Identifier # to the IRB prior to IRB approval.NCT #:
YES	**NO**	**NIH Requirements**
☐	☒	Does your study meet the definition of an applicable clinical trial and require registration **AND** results submission in accordance with NIH? For more information on this policy please refer to: • NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information • Checklist **Note:** If your study meets the requirement for registration and reporting, you must submit the National Clinical Trial (NCT) Identifier # to the IRB prior to IRB approval. NCT #:

Certification / Signatures

- By submitting this protocol I attest to the fact that all research activities to be implemented related to human subjects have been completely and accurately described herein.
- I agree to conduct the describe research in an ethical manner.
- I agree to comply with all institutional policies and procedures related to human subjects research and will not begin any human subjects research activities until I have obtained full approval from the IRB.
- I agree to conduct the research as described in this protocol and not to make any changes (except to eliminate immediate harm to subjects) without first obtaining approval for the changes from the IRB.
- I agree to immediately report any unanticipated problems involving risks to subjects or others, any subject complaints, and any incidents of non-compliance with the requirements of this protocol as soon as I become aware of them.
- I agree to comply with any relevant HIPAA and FERPA regulations if applicable.
- I verify that all those responsible for the design, conduct, or reporting of the proposed program, including at minimum, all Senior/key personnel in the grant application, have completed the financial interest disclosure forms and completed training as dictated at http://www.bu.edu/orc/coi/forms/, and returned the forms to the Office for Research Compliance COI Unit. **NOTE: If anyone checked "yes" to any of the questions on either the FIND1 or NONFIND1 form, the IRB Director will contact the COI office to obtain the disclosure information.**

PI Printed Name: Louis Awad

PI Signature:  **Date: July 07, 2021**

Submission: This form can be completed, signed, scanned and submitted to the IRB at irb@bu.edu. Faxed documents and handwritten materials are not accepted. Be sure to include all relevant attachments.