#20194936 - BCI-FES therapy for stroke rehabilitation

Protocol Information

Review Type	Status	Time in Current Status	Submission Number
Full Board	**Expired**	**Since October 18 – a year**	**16**

Approval Date	Continuing Review Date	Expiration Date	Initial Approval Date
Oct 11, 2024	--	**Oct 10, 2025**	**Jan 08, 2021**

Initial Review Type

Full Board

Protocol Renewal Form

Renewal Information

Protocol Type

Are you submitting a renewal for an IRB, sIRB, or hSCRO protocol?

IRB (UCI is the IRB of Record)

IRB Renewal Instructions

Timing of Submission

Exempt and Expedited IRB protocols must submit a short version of the renewal every three (3) years unless determined otherwise by the IRB. Investigators should plan ahead and submit 60 days prior to the study's expiration date.

Full Committee IRB protocols must submit a renewal at least annually (not more than 365 days). Investigators should plan ahead to meet required continuing review dates. For full committee review protocols, please submit 90 days prior to the expiration date to guard against a lapse in IRB approval.

Amendments at the Time of Renewal

Please refrain from making major changes during the renewal as this could result in a lapse of IRB approval.

Protocol Closure

To close out an approved protocol at the time of renewal, the transaction must be submitted as Request Close. If this option was not initially selected and closure is required, please Abandon the draft and start again. For more information, visit Post-Review Responsibilities and select the Protocol Renewal Tab.

Renewal Screener

Does any of the following apply to the currently approved protocol:

- **research involves Greater than Minimal Risk (Full Committee)**
- **research is subject to Food and Drug Administration (FDA) regulations**
  - **Involves a drug**
  - **A clinical investigation of a medical device**
- **research is funded/supported by the Department of Justice (DOJ)**
- **current approval period is 1 year or less**

Yes (Continuing Renewal Required)

Protocol Expiration

Protocol Expiration

Has approval for this protocol expired or will it expire within 3 weeks?

No

Confirmation of Protocol

Study Team

Review the Study Team Section and consider whether anyone should be removed at this time via an Amendment.

RP Heat Map

Are RP tracked outside the approved protocol, in accordance with the RP Heat Map?
Yes, RP are tracked on a Study Team Log or other comparable log

Financial Interests

Review the Study Team section and specify below if there have been any changes in the study team's related financial disclosable interests.

See Conflict of Interest Oversight Committee (COIOC) for more details.
No, there have been no changes to the study's teams related disclosable financial interests

Relying Non-UCI Entity (as applicable)

When UCI is the IRB of Record for a non-UCI entity (i.e., site or independent investigator), review the sIRB section and remove any non-UCI entities (site or independent investigator) that are no longer *engaged* in research via an Amendment.

Clinicaltrials.gov Status

ClinicalTrials.gov Registration

Does this research meet the definition of a clinical trial that requires adherence to Clinicaltrials.gov (CT.gov)?
Yes

Confirm the accuracy of ClinicalTrials.gov section in the IRB protocol (select one):

Please review the ClinicalTrials.gov section in the IRB protocol to verify that the information is still accurate.

If any revisions are required, please submit an amendment to request a 'Change in Clinicaltrials.gov' and update the the protocol accordingly.

As lead researcher, I confirm that the CT.gov information is accurate as indicated in the protocol

Specify who is responsible for registering, maintaining, and updating the CT.gov record:

UCI Investigator

Confirm the accuracy of the information on the ClinicalTrials.gov Protocol Registration and Results System (PRS):

IMPORTANT! Per federal requirements (42 CFR 11.64(a)(1)(ii)), clinical trial registration information on PRS must be updated not less than once every 12 months.

Please review the information on PRS to verify that the following fields are accurate and up to date:

- **Study Status:**
  - **Record Verification Date: Not less than every 12 months, enter the date on which the responsible party last verified the clinical study information on PRS, even if no additional or updated information was submitted.**
  - **Overall Recruitment Status: 30 calendar days after a change in overall recruitment status, enter the status for the clinical study as a whole, based upon the status of the individual sites. If at least one facility in a multi-site clinical study has a status of "Recruiting," then the overall status for the study must be "Recruiting."**
  - **Primary Completion Date: 30 calendar days after the clinical trial reaches its actual primary completion date, enter the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. IMPORTANT! This date cannot be in the past, please revise the date as necessary.**
  - **Study Completion Date: 30 calendar days after the clinical trial reaches its actual study completion date, enter the date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant's last visit), whether the clinical study concluded according to the pre-specified protocol or was terminated. IMPORTANT! This date cannot be in the past, please revise the date as necessary.**
- **Oversight:**
  - **Human Subjects Review Board Status: 30 calendar days after a change in status, ensure the status of IRB approval information is accurate.**
- **Contacts, Locations, and Investigator Information: 30 calendar days after a change, ensure the information is accurate.**

As leader researcher, I confirm that the clinical trial information (listed above) on PRS is accurate and up to date.

Enrollment Status

Accruals

Please mark the option that represents the current status of subject enrollments:
Enrollment closed - research procedures ongoing

Subject Enrollments

Please confirm the total number of subjects (i.e. individuals, specimens, records) approved by the UCI IRB in the Subject Populations section.

Indicate the number of new subjects enrolled since last IRB review:
32

Indicate the total number of subjects (including the number in the previous question) enrolled since initial UCI IRB approval:
191

Did the total number of subjects enrolled to date exceeds the total number approved by the IRB?
No

Indicate the total number of subjects enrolled per group since initial IRB approval:

Man (total):
120

Woman (total):
71

Nonbinary (total):
0

Not Collected (total):
0

Adults (total):
191

Minor (total):
0

Multi-Center Studies: If known, indicate the total number of subjects enrolled at ALL sites to date:
Not applicable

Subject Withdrawals

Early Termination(s)

Did the Lead Researcher or a Co-Researcher remove any subject(s) from the study?
Yes

Please provide the reason(s) here (e.g., failed to follow instructions, missed appointment, medical complications, subject safety issue):
1 subject was removed from the study by the physician due to inability to tolerate the treatment.

Voluntary Withdrawal(s)

Did any subject(s) voluntarily withdraw from the study?
Yes

Please describe the reason(s) here (e.g., relocation; dissatisfaction):

1 subject withdrew from study due to inability to commit to the treatment schedule.

Reportable Events

Reportable Events

Have there been any problems that required prompt reporting to the UCI IRB?

No problems that require reporting

Complaints

Have there been any complaints from UCI participants or others that required reporting to the UCI IRB?

No

Progress Report

UCI Progress

Please provide a detailed description of the progress of the study, including a brief summary of any interim findings or trends, and plans for the next approval period:

Our phase 2 clinical trial has concluded recruitment, enrollment and treatment. The plan for the next approval period is to complete post treatment assessments and data analysis. Interim data was reviewed confidentially by the DSMB at their meeting in November 2023 and approved. The DSMB Meeting report was uploaded to the attachment section. Subject status breakdown: Aim 1: 168 assessed for eligibility; 106 were ineligible, 62 were randomized to study; 54 received intervention per protocol and completed all assessments, 1 withdrew from treatment but completed assessments, 4 withdrew consent from study, 2 were removed by physician; 1 is ongoing for final assessment; Aim 3: 23 assessed for eligibility; 13 were ineligible, 10 were randomized to study; 8 received intervention per protocol and completed all assessments, 0 withdrew from treatment but completed assessments, 0 withdrew consent from study, 0 were removed by physician; 2 are ongoing for final assessment. Aims 1 and 3 were the only 2 aims that were enrolling subjects and have closed enrollment. Clinicaltrials.gov has been updated to reflect close of enrollment.

Relying Entity Progress (as applicable)

If UCI is the IRB of Record for a non-UCI entity, provide a progress report for each relying entity (e.g., number of participants enrolled at the sub-site; data analysis performed, if any, etc):

Not applicable

Sponsor Multi-Center Progress (as applicable):

Is a multicenter progress report / newsletter is available from the Sponsor?
Not Applicable

Informed Consent

Confirm that there is no new information that raises concerns about the circumstances under which informed consent is being obtained:
No new information

Confirm that any new findings that have developed since the last continuing review, have been provided to enrolled subjects, as appropriate:
No new findings

Confirm that the research team is using the most recently approved version of the consent/assent document and that it contains the most accurate, up-to-date information about the research:
Yes

Confirm that all signed consent documents are on file and available for inspection:
Yes

Specify if any subjects were enrolled using a non-English consent document, information sheet, or script:
No

Given that some research studies have multiple consent/assent forms, please indicate which approved consent/assent forms should be reviewed by the IRB:
Review all consent/assent forms

Re-Consent Status

Since the last IRB Approval, did any Amendments require subjects to be re-consented?
No

Internal and External Audits

Internal Audit(s)

Have any internal (UCI/UCI Health) audits occurred since last IRB review?
No

External Audit(s)

Have any external (FDA/OHRP/Sponsor) audits occurred since last IRB review?
No

Risk and Safety Assessments

Relevant Recent Literature

During the past year has there been anything in relevant literature that the IRB should consider when reviewing this application for continuing approval?

No

Current Risk/Benefit Assessment

Has there been a change in risk/benefit?

Take into account the information gathered during the past year such as interim results, reportable events/problems, changes in scientific knowledge, and/or relevant regulatory actions regarding study-wide safety and/or efficacy (e.g., product recall). This assessment should be sufficiently detailed to assist the IRB in determining whether continuation of IRB approval is appropriate.

No

Data Safety Monitoring Board (DSMB)

Has there been any new DSMB findings relating to subject safety?

No new findings related to subject safety

Investigator's Brochure (IB)

For FDA regulated drug studies, enter the current version number and date of the Investigator's Brochure in the Supplemental Documents section.

End of renewal form!

IMPORTANT! Go to the next section to complete the amendment form.

Protocol Amendment Form

Amendment Instructions

Specify the type of submission:

RENEWAL: This is a renewal that does not require changes to the approved protocol

End of amendment form!

Project Details

Specify the study title (this title should not exceed more than 100 words):

BCI-FES therapy for stroke rehabilitation

Lead Researcher/Investigator:

An Hong Do

Enter the Lead Unit:

IR-7455 - NEUROLOGY (Lead Unit)

Project Screener

Submit a Human Subject Protocol for UCI Institutional Review Board (IRB) Review

Will this protocol be reviewed under a sIRB process?

No, there is no reliance involved. UCI serves as the IRB of record

Are the research procedures limited to the use/analysis of identifiable private information and/or identifiable biospecimens (no subject contact)?

No

Select the required level of review for this protocol:

Greater than Minimal Risk (Full Committee)

Check all sites where UCI investigator(s) will conduct research activities (e.g., recruitment, informed consent, and research procedures including accessing identifiable, private information about participants):

UCI Facilities or Sites (e.g. school, hospital or clinics, etc.)

Provide a non-technical summary of the project that can be understood by IRB/hSCRO members with varied research backgrounds, including non-scientists and community members (this summary should not exceed more than 250 words):

There are over 7 million stroke survivors in the US alone, with approximately 795,000 new cases annually. Despite the best available physiotherapy, 30-60% of stroke survivors remain affected by difficulty walking, with foot weakness often being the main cause. Given that post-stroke gait impairments remain poorly addressed, new methods that can provide lasting improvements are necessary. Brain-computer interface (BCI) technology may be one such novel approach. BCI technology enables “direct brain control” of external devices such as assistive devices and prostheses by translating brain waves into control signals. When BCI systems are integrated with functional electrical stimulation (FES) systems, they can be used to deliver a novel physical therapy to improve movement after stroke. BCI-FES systems are hypothesized to stimulate recovery after stroke beyond that of conventional physical therapy. Preliminary research indicates that applying this technique to foot weakness after stroke is safe and may improve walking function. Hence, this warrants further investigation to: 1. determine if BCI-FES therapy can provide lasting gains in walking in chronic stroke patients; 2. determine what factors influence BCI-FES therapy; and 3. explicitly elucidate the underlying neural repair mechanisms. First, a Phase II clinical trial in patients with foot drop due to chronic stroke will compare the effect of BCIFES dorsiflexion therapy to that of dose- and intensity-matched standard physical therapy (Aim 1). Comparing the improvement in walking speed and other secondary outcome measures between the two groups will test if BCI-FES therapy provides functional and neurological gains beyond those of standard physical therapy. The relationship between the patient baseline characteristics (walking speed, ankle function, stimulated muscle responses, brain wave features, sensation) and the outcomes will determine what features influence responsiveness to BCI-FES dorsiflexion therapy (Aim 2). Finally, the underlying mechanism driving the improvements of BCI-FES will be studied (Aim 3). Determining that BCI-FES therapy can provide improvements beyond that of standard therapy may lead to a new treatment for stroke patients. The underlying mechanism can inform the design of future physical therapy techniques or improve current ones. Finally, BCI-FES therapy may ultimately become a novel form of

physical therapy to reduce post-stroke disability, and in turn reduce the public health burden of stroke.

Instructions

IRB Protocol Instructions

- **For research with a Master Protocol or with a detailed project proposal, specify this in the protocol and an abbreviated protocol will be generated.**
- **Submit all new and/or revised supporting documents in the Protocol Attachments section near the end of the protocol.**
- **The Lead Researcher (LR) is responsible for maintaining all supplemental documentation (as indicated in the form) in the research records. This documentation may be requested by Human Research Protections for quality assurance review.**

For regulatory or institutional guidance:

- **Visit Human Research Protections**
- **Contact the Human Research Protections staff**

For technical issues or questions:

- **Visit the Kuali Research Protocols (KRP) User Guide**
- **Contact Electronic Research Administration (ERA)**

Type of Research

The purpose, specific aims or objectives of the research is:

Biomedical

The research protocol is:

Investigator-Initiated

Does the investigator-initiated study have any industry support?

No

Does this study include a Master Protocol or detailed project proposal?

No

Is this study an extension of a UCI IRB approved study (e.g., resubmission of ongoing exempt research; Open Label Extension) or is it otherwise related to a UCI IRB approved study?

No

Does this research meet the definition of a clinical trial that requires adherence to Clinicaltrials.gov?

Yes

If currently available, provide the CT.gov registration NCT # (**Enter 8-digit sequence of numbers only**):

04279067

Specify the rationale for Clinicaltrials.gov registration:

NIH-funded Clinical Trial

STOP! All clinical trials must be conducted under the auspices of an Organized Lead Unit (OLU). Please update. Go to Project Details and choose the appropriate OLU for the trial.

Study Funding

Select the funding source(s) (**check all that apply**):

Grant/Contract

No Campus or Extramural funding

Select the sponsor type(s) (**check all that apply**):

Health and Human Services (HHS) (includes National Institutes of Health (NIH)

List below all extramural proposals or awards that will support the study (if applicable):

IMPORTANT! Skip this table if extramural funding is not available.

Sponsor Name

NIH

Title of Proposal/Award (if different from study title):

Proposal or Award #:

Scientific/Scholarly Review

Is the research Sponsor-Initiated?

Yes

The proposed research qualifies as greater than minimal risk, sponsor-initiated biodmedical research. It is assumed that scientific merit has been conducted. Available peer review comments may be requested by the IRB for consideration.

Greater than Minimal Risk Non-Cancer, Sponsor Initiated Biomedical Research - Received Peer Review

Data Safety Monitoring Plan

Does this protocol require a DSM plan?

Yes

Provide details of those individuals who will be responsible for the safety oversight of your protocol, including the relevant experience/expertise of each individual (for UCI investigator initiated studies conducted only at UCI, provide the names and titles as well):

- Dr. Gaby Thai, MD (Associate Professor, Department of Neurology, UCI - a neurologist with over 10 years in clinical trial experience) - Dr. Kelli Sharp, DPT, PhD (Professor, Department of Dance, UCI - a clinical research physical therapist with extensive clinical trials experience for rehabilitation technologies). - Dr. Luohua Jiang, PhD – a biostatistician with clinical trial experience will analyze the data accrued so far and present the findings to the DSMB

Indicate how frequently accumulated protocol data will be reviewed and evaluated for participant safety, protocol conduct and progress, and, when appropriate, efficacy:

- DSMB will meet to review results after each time 26 subjects are recruited (~one-third of the recruitment goal) during Aim 1. Note that Aim 2 relies on the subjects from Aim 1. Aim 3 is not a clinical trial and hence will not be subjected to this.

Describe the events that would trigger an unscheduled review. Also include stopping guidelines and un-blinding rules if applicable:

- An unscheduled review can be triggered by an event in which a serious adverse and unanticipated problem arose that was deemed related to the study. This may include serious injury due to fall, or even death, that was related to the study intervention. - The DSMB will be advised of the following stopping criteria: 1. if the proportion of subjects experiencing falls in those receiving BCI-FES therapy begins increases significantly (i.e. >10%) or if the fall rate amongst subjects in the BCI-FES group increases significantly from baseline; 2. More than 10% of subjects in the BCI-FES group experience a decrement in gait velocity of >0.16 m/s. Additional specific stopping points will not be prespecified, rather the judgment of the DSMB will be respected.

List who will be *locally* monitoring and collecting information on adverse events and/or unanticipated problems (e.g., UCI Lead Researcher, Research Coordinator, etc.). Include the name, title and experience of the individual(s) and further describe each individual's role in the oversight of subject/patient participating in the protocol:

- The lead researcher, Dr. An Do, and the study coordinator, Lucy Dodakian, will be responsible for collecting information on adverse events and/or unanticipated problems.

Describe the plan for annual reporting of the participants' safety, and the protocol's conduct, progress, and efficacy, when appropriate:

- All relevant clinical data will be presented to the IRB on a yearly basis, including reports of the DSMB, including serial gait velocity, dorsiflexion range of motion and torque, leg motor Fugl-Meyer score, gait endurance test, and fall frequency. The investigative team will be blinded to these, so they will be submitted directly from the DSMB to the IRB.

Potentially Hazardous Materials

If any of the following hazardous materials are involved in this research please check below:

N/A

Other UCI Committee Reviews

Check all ancillary committees that apply:

N/A

Study Team

Study Team:

- **List only study team members who are engaged in human subjects research below.**
    - **Administrative Contact (AC): Do not add ACs to the study team table. To add ACs, navigate to the Permissions tab on top-right-hand-side of form. All ACs must complete the requisite Human Research Protections CITI Training.**
- **Lead Researcher (LR): LRs must meet requirements specified on the Lead Researcher Eligibility page for study to be approved.**
    - **Select 'Oversight of Research' along with other applicable duties.**
    - **Select 'Full Access'.**
- **Faculty Sponsor (FS): FSs are required when the person serving the LR role is not qualified to serve as LR-- the FS must be eligible to be LR.**
    - **Select 'Oversight of Research' along with other applicable duties.**
    - **Select 'Full Access'.**
- **Co-Researcher (CR): CRs are faculty, staff, students and other academic appointees who the LR considers to be key personnel for conducting the research study. These individuals work closely with the LR to design, conduct, and/or report on the research.**
- **Research Personnel (RP): List RP as required per the Research Personnel Heat Map. For those RP who do not need to be listed on the protocol, they may be tracked by alternative methods, see below.**
- **IMPORTANT! Do NOT list non-UCI researchers below, in the Permissions tab at top or on the Study Team Tracking Log (or equivalent); instead, follow the Single IRB Reliance (sIRB) process.**
- **Collaborative Institutional Training Initiative (CITI) Human Research Protections Training Courses**
    - **Confirm CITI training is complete and current for all study team members.**
    - **Incomplete or expired CITI training will delay IRB approval.**
    - **For more information, visit HRP Training and Education.**

Researcher

An Hong Do

Training

GCP for Clinical Investigations of Devices - Refresher Course 03/23/17 - 03/22/20 Expired	GCP for Clinical Investigations of Devices - Basic Course 11/10/22 - (no expiration)
GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Basic Course 10/26/21 - 10/25/24 Expired	GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Refresher Course 03/23/17 - 03/22/20 Expired
Biomedical Investigators - Refresher Course	11/10/22 - (no expiration)

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

MD

Degree Other

Position/Title

Assistant Professor

Department

IR-7455 - NEUROLOGY (Lead Unit)

Affiliation
UCI Faculty

Specify other UCI affiliation:

Researcher Role

Lead Researcher

Permissions

Full Access

Duties

Oversight of Research
Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information
Access/Analyze Identifiable Biospecimens

Describe additional research procedures below:
Will be involved in: - Subject screening, recruitment - Data analysis - BCI procedures - Electrophysiological procedures (EEG, EMG) - Safety oversight for participants in all groups of the study

Specify relevant training and experience for the referenced duties/responsibilities:
Medical degree, neurology, neurophysiology, clinical rehabilitation. He will also be finalizing the consent as he has extensive experience, expertise and training in clinical research and consenting patients and can answer any questions the patients may have prior to deciding to participate, regarding the risks/safety related to the devices used in this study, including medical-related information.

Researcher

Steven c Cramer

Training

UCI Biomedical Research Investigators - Basic Course	02/26/09 - (no expiration)

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

MD

Degree Other

Position/Title

Adjunct Professor, Neurology

Department

IR-7455 - NEUROLOGY (Lead Unit)

Affiliation

UCI Faculty

Specify other UCI affiliation:

Researcher Role

Co-Researcher

Permissions

Full Access

Duties

Research Procedures
Access/Analyze Identifiable Information
Access/Analyze Identifiable Biospecimens

Describe additional research procedures below:

Will be involved in: Overseeing design and implementation of study, data analysis with access to de-identified data, overseeing design of conventional physical therapy regimen, TMS procedures

Specify relevant training and experience for the referenced duties/responsibilities:

Medical degree, neurology, stroke, rehabilitation

Researcher

David J Reinkensmeyer

Training

GCP for Clinical Investigations of Devices - Refresher Course 12/16/20 - 12/16/23 Expired	GCP for Clinical Investigations of Devices - Basic Course 12/15/23 - (no expiration)
Biomedical Investigators - Basic Course	03/23/22 - 03/22/27

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

PhD

Degree Other

Position/Title

Professor, Anatomy and Neurobiology

Department

IR-8095 - MECHANICAL ENGINEERING

Affiliation

UCI Faculty

Specify other UCI affiliation:

Researcher Role

Co-Researcher

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information
Access/Analyze Identifiable Biospecimens

Describe additional research procedures below:
Will be involved in: - Subject screening, recruitment - Data analysis - BCI procedures

Specify relevant training and experience for the referenced duties/responsibilities:
Mechanical engineering, rehabilitation engineering. He will also be finalizing the consent as he has extensive experience, expertise and training in clinical research and consenting patients and can answer any questions the patients may have prior to deciding to participate, regarding the risks/safety related to the devices used in this study, including medical-related information.

Researcher

Zoran Nenadic

Training

GCP for Clinical Investigations of Devices - Refresher Course 08/10/22 - (no expiration)	GCP for Clinical Investigations of Devices - Basic Course 03/08/19 - 03/07/22 Expired
GCP - Social and Behavioral Research Best Practices for Clinical Research - Basic Course 08/11/22 - (no expiration)	GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Basic Course 03/08/19 - 03/07/22 Expired
GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Refresher Course 08/10/22 - (no expiration)	Biomedical Investigators - Basic Course 03/02/17 - 03/01/22 Expired
Biomedical Investigators - Refresher Course	08/10/22 - (no expiration)

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

“Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

Other

Degree Other

DSc

Position/Title

Professor, Biomedical Engineering

Department

IR-8098 - ENGINEERING/BIOMEDICAL ENGINEERING

Affiliation

UCI Faculty

Specify other UCI affiliation:

Researcher Role

Co-Researcher

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information
Access/Analyze Identifiable Biospecimens

Describe additional research procedures below:

Will be involved in: - Subject screening, recruitment - Data analysis - BCI procedures - Electrophysiological procedures (EEG, EMG)

Specify relevant training and experience for the referenced duties/responsibilities:

Biomedical engineering and signal analysis. He will also be finalizing the consent as he has extensive experience, expertise and training in clinical research and consenting patients and can answer any questions the patients may have prior to deciding to participate, regarding the risks/safety related to the devices used in this study, including medical-related information.

Researcher

Danh Van Nguyen

Training

Danh Nguyen has no training courses on file.

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

PhD

Degree Other

Position/Title

Professor, Internal Medicine

Department

IR-6101 - MEDICINE - DIVISION OF GENERAL INTERNAL MEDICINE & PRIMARY CARE (Lead Unit)

Affiliation

UCI Faculty

Specify other UCI affiliation:

Researcher Role

Co-Researcher

Permissions

Full Access

Duties

Research Procedures
Access/Analyze Identifiable Information
Access/Analyze Identifiable Biospecimens

Describe additional research procedures below:
Data Analysis

Specify relevant training and experience for the referenced duties/responsibilities:
Biostatistics and clinical trial design

Researcher

Alison L Mckenzie

Training

Alison Mckenzie has no training courses on file.

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"
No

Degree

Other

Degree Other

PT, DPT, PhD

Position/Title

Project Scientist Department of Neurology

Department

IR-7455 - NEUROLOGY (Lead Unit)

Affiliation

UCI Faculty

Specify other UCI affiliation:

Researcher Role

Co-Researcher

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information

Describe additional research procedures below:

see below

Specify relevant training and experience for the referenced duties/responsibilities:

Dr. Alison McKenzie is a collaborating physical therapist from Chapman University. She has dual appointments at UC Irvine and Chapman University. She will help with protocol development and implementation, recruitment, data acquisition and analysis. She will also be involved in subject screening, administer stroke outcome measures and assessments, Electrophysiological procedures (EEG, EMG) and TMS procedures. She will also be finalizing the consent as she has extensive experience, expertise and training in clinical research and consenting patients and can answer any questions the patients may have prior to deciding to participate, regarding the risks/safety related to the devices used in this study, including medical-related information.

Researcher

Lucy Dodakian

Training

UCI Biomedical Research Investigators - Refresher Course
11/14/19 - 11/13/22
Expired

GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Basic Course
11/14/23 - (no expiration)

GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Refresher Course
12/11/20 - 12/11/23
Expired

Biomedical Investigators - Basic Course
10/07/22 - (no expiration)

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

MA

Degree Other

Position/Title

Research Occupational Therapist

Department

Physical Therapy - IP

Affiliation

UCI Staff

Specify other UCI affiliation:

Researcher Role

Research Personnel

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information

Describe additional research procedures below:
- Study coordination - Subject recruitment - Administrative contact

Specify relevant training and experience for the referenced duties/responsibilities:
Training in clinical and research occupational therapy, extensive experience in coordinating and conducting clinical studies and clinical trials. She will also be finalizing the consent as she has extensive experience, expertise and training in clinical research and consenting patients and can answer any questions the patients may have prior to deciding to participate, regarding the risks/safety related to the devices used in this study, including medical-related information.

Researcher

WaiKi Vicky Chan

Training

GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Basic Course
11/17/23 - (no expiration)

GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Refresher Course
12/18/20 - 12/18/23
Expired

Biomedical Investigators - Basic Course
09/30/24 - (no expiration)

Biomedical Investigators - Refresher Course
10/14/19 - 10/12/24
Expired

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

Other

Degree Other

DPT

Position/Title

Research Physical Therapist

Department

Physical Therapy - IP

Affiliation

UCI Staff

Specify other UCI affiliation:

Researcher Role

Research Personnel

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information

Describe additional research procedures below:

- Subject screening, recruitment - Administer stroke outcome measures and assessments - Electrophysiological procedures (EEG, EMG) - TMS procedures - will be finalizing consent for Groups 3&4 Consent Procedures

Specify relevant training and experience for the referenced duties/responsibilities:

Training in clinical and research physical therapy and assessments/devices used in this study. She will also be finalizing the consent as she has extensive experience, expertise and training in clinical research and consenting patients and can answer any questions the patients may have prior to deciding to participate, regarding the risks/safety related to the devices used in this study, including medical-related information.

Researcher

Jill See

Training

GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Basic Course 08/31/23 - 08/31/26	GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Refresher Course 09/09/20 - 09/09/23 Expired
IRB-Mandated Compliance - Biomedical	09/26/24 - 09/26/29

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

Other

Degree Other

DPT

Position/Title

Research Physical Therapist

Department

Physical Therapy - IP

Affiliation

UCI Staff

Specify other UCI affiliation:

Researcher Role

Research Personnel

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information

Describe additional research procedures below:
- Subject screening, recruitment - Administer stroke outcome measures and assessments - Electrophysiological procedures (EEG, EMG) - TMS procedures

Specify relevant training and experience for the referenced duties/responsibilities:
Training in clinical and research physical therapy and assessments/devices used in this study. She will also be finalizing the consent as she has extensive experience, expertise and training in clinical research and consenting patients and can answer any questions the patients may have prior to deciding to participate, regarding the risks/safety related to the devices used in this study, including medical-related information.

Researcher

Sharada Sripathi Govindu

Training

GCP for Clinical Investigations of Devices - Basic Course 02/15/22 - 02/14/25 Expired	Biomedical Investigators - Basic Course 02/10/22 - 02/09/27
Research and HIPAA Privacy Protections	02/08/22 - 02/07/27

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

Other

Degree Other

DPT

Position/Title

Research Physical Therapist

Department

Physical Therapy - IP

Affiliation

UCI Staff

Specify other UCI affiliation:

Researcher Role

Research Personnel

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information

Describe additional research procedures below:
Subject Screening, recruitment; Administer stroke outcome measures and assessments; Electrophysiological procedures (EEG, EMG), will be finalizing consent for the Screening and Groups 1&2 Consent Procedures.

Specify relevant training and experience for the referenced duties/responsibilities:
Training in clinical and research physical therapy and assessments/devices used in this study. She will also be finalizing the consent as she has been trained in clinical research and consenting patients and can answer any questions the patients may have prior to deciding to participate, regarding the risks/safety related to the devices used in the study.

Researcher

Heather B Carter

Training

GCP for Clinical Investigations of Devices - Basic Course
06/14/23 - (no expiration)

Biomedical Investigators - Basic Course
06/13/23 - (no expiration)

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

Other

Degree Other

OT R/L (Masters); BA in Ecology

Position/Title

Research Occupational Therapist

Department

Physical Therapy - IP

Affiliation

UCI Staff

Specify other UCI affiliation:

Researcher Role

Research Personnel

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information

Describe additional research procedures below:
Subject screening, recruitment; Administer stroke outcome measures and assessments; Electrophysiological procedures (EEG, EMG), will be finalizing consent for the Screening and Groups 3&4 Consent procedures.

Specify relevant training and experience for the referenced duties/responsibilities:
Training in clinical and research occupational therapy and assessments/devices used in this study. She will also be finalizing the consent as she has been trained in clinical research and consenting patients and can answer any questions the patients may have prior to deciding to participate, regarding the risks/safety related to the devices used in the study.

Are RP tracked outside the approved protocol, in accordance with the RP Heat Map?
Yes, RP are tracked on a Study Team Log or other comparable log

Supplemental Documents

Does this study include supplemental documents?
No

Background & Purpose of the Research

Describe the purpose, specific aims or objectives and specify the hypotheses or research questions to be studied:

Aim 1: Quantify the neurological and functional improvements due to BCI-FES dorsiflexion therapy compared to dose- and intensity-matched conventional therapy. Hypothesis: The neural repair mechanisms underlying BCI-FES dorsiflexion therapy will lead to improvements in neurological and functional outcomes that are greater and longer-lasting than those achieved by dose-matched conventional therapy. Aim 2: Identify stroke features that are linked to responsiveness to BCI-FES dorsiflexion therapy. Hypothesis: Based on preliminary studies, baseline gait velocity, dorsiflexion AROM/torque, TA muscle electromyogram (EMG) and motor evoked potentials, the magnitude of EEG alpha- and beta-band ERD/ERS during attempted dorsiflexion, and sensory function will influence the response to BCI-FES dorsiflexion therapy. Aim 3: Investigate the mechanism of action of BCI-FES dorsiflexion therapy. Hypothesis: BCI-FES therapy reinforces the connectivity between foot M1 and the α-MN due to Hebbian plasticity. The study will have a significant impact in rehabilitative neuroscience, clinical neurorehabilitation,

Provide the scientific or scholarly rationale for the research and describe the relevant background information and the specific gaps in current knowledge that this study intends to address:

There are >7 million stroke survivors in the US alone, with approximately 795,000 new cases annually. Despite spontaneous recovery and the best available physiotherapy, between 30% and 60% of stroke survivors remain affected by gait function impairments [2, 3], with foot-drop often being the primary cause. Chronic poststroke gait impairments are: 1. associated with significant disability and reduced physical activity; 2. directly linked to poor social re-integration; and 3. ranked as the top rehabilitation priority among stroke survivors. These problems lead to an increased risk of medical complications and raise a major public health concern due to increased healthcare, caregiving, and lost productivity costs. These costs are expected to increase as the aging population grows and acute stroke survival rates keep improving. Clinicians have for decades utilized biomechanical methods such as ankle-foot orthoses (AFO) and functional electrical stimulation (FES) orthoses to mitigate post-stroke gait impairment. However, these devices are cumbersome, may cause discomfort, and their benefits disappear upon removal. Consequently, post-stroke gait impairments remain suboptimally addressed. Novel methods that are based on neurobiological principles and can provide lasting neurological and functional improvements are therefore necessary [9]. This is particularly needed for stroke survivors with the worst neurological functions, whose impairments are too severe to participate in most rehabilitative therapies. Such methods would improve the function of the affected individuals to the point where they could participate in both existing and novel physiotherapies. This outcome would improve the quality of life and increase independence of the affected population. It would also reduce the overall cost. Brain-computer interface (BCI) technology may be one such novel approach to post-stroke rehabilitation. Noninvasive BCIs perform real-time analysis of brain signals, e.g. electroencephalogram (EEG), and translate these into control commands for assistive devices. For example, when integrated with FES systems, BCIs could be used to deliver a novel form of post-stroke physiotherapy. We hypothesize that such a therapy can stimulate a Hebbian plasticity process (“neurons that fire together, wire together”), and thereby improve poststroke plasticity and functional recovery beyond those of conventional physiotherapy. Specifically, by modulating EEG, a user can trigger FES of the impaired limb. This provides a co-incident activation of the post-stroke motor cortex, M1, (detected by BCI) and the

corresponding spinal motor pools (via antidromic electrical stimulation of peripheral motor neurons, alpha MN), which over time may reinforce their connections. Since therapeutic gains in motor function are generally accompanied by favorable forms of motor system plasticity, such hypothesized changes due to BCI-FES therapy may translate into enduring functional gains, possibly even in those who do not rehabilitate naturally. Early feasibility studies of this BCI-FES concept in the upper and lower extremity rehabilitation, suggest that this approach is safe and can significantly improve post-stroke motor function. Using foot-drop as a post-stroke deficit model, the applicants undertook four preliminary studies to engineer a reliable BCI-FES system for foot dorsiflexion and demonstrate the BCI-FES system's safety and potential to promote neurological recovery after stroke.

Provide relevant preliminary data (animal and/or human):

We performed a long-term study to assess the safety and potential of BCI-FES therapy. Nine chronic stroke subjects (>6 months post-ictus) with gait impairment due to foot-drop underwent 12 sessions of BCI-FES therapy (3 sessions/week, for 4 weeks). The primary outcome measure was gait velocity. Secondary outcomes were dorsiflexion active range of motion (AROM), leg motor Fugl-Meyer score, gait endurance (6-min walk test), and fall frequency. These outcomes were assessed before, on a weekly basis, and 1 month after completion of the BCI-FES therapy (Fig. 3). No subjects experienced a significant decrement in any outcome measure and there were no adverse events, indicating that BCI-FES therapy is safe. In post-hoc analysis, 6 out of 9 (66.7%) subjects had a significant improvement in gait velocity at 1 month post-therapy (average increase of 51%, or 0.21 +/- 0.15 m/s). While no spatial cortical reorganization was observed in any subject at the end of therapy, the Cz channel (electrode over the foot motor area) exhibited an increase in alpha- and beta-band event-related desychronization/synchronization (ERD/ERS) magnitude in 5 of these 6 (83.3%) subjects. Conversely, these EEG changes did not occur in the 3 subjects with no gait velocity improvement. This suggests the existence of a neural process underlying gait velocity improvements. Subjects with low gait velocity (<0.4 m/s) and poor dorsiflexion AROM (<5 degrees) at baseline were 150% more likely than those with moderate-to-high gait velocity (>0.4 m/s) or good-to-excellent AROM (>5 degree) to experience an increase in gait velocity. This highlights a potential promise of BCI-FES therapy in that it may be accessible and beneficial to stroke survivors whose baseline motor functions are too low for current or emerging interventions.

Describe the primary outcome variable(s), secondary outcome variables, and predictors and/or comparison groups as appropriate for the stated study objectives/specific aims:

The primary outcome measure will be gait velocity, which is directly linked to disability and social re-integration after stroke. Gait velocity will be assessed by measuring the time to traverse the middle 6 m of a 10-m walkway (5 repetitions/assessment). Secondary outcomes include: 1. Gait endurance: The distance walked over 6 minutes. 2. Fall Frequency: Number of falls experienced weekly. 3. Leg Motor Fugl-Meyer (FM) Score: Assessed according to the FM rating system. 4. Dorsiflexion Active Range of Motion (AROM) and torque: The paretic foot will be placed in an articulated brace which maintains the ankle at neutral during idling, while fixing the tibia perpendicular to the ground and the femur horizontal to the ground. The brace will be instrumented with an electro-goniometer and torque meter to automatically measure the maximum dorsiflexion AROM and torque (over 3 trials). 5. EEG Map: Subjects will undergo 64-channel EEG recording as they engage in 100 alternating 10-s long epochs of idling and attempted dorsiflexion. The EEG ERD/ERS, defined as the drop/rise in alpha (8-12 Hz) and beta (13-30 Hz) band power during attempted dorsiflexion (compared to idling), will be calculated and averaged over all epochs and across all channels.

List up to ten relevant references/articles to support the rationale for the research:

• Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation. 2012;125(1):e2–e220. • Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM. Brain-computer interfaces for communication and control. Clin Neurophysiol. 2002;113(6):767–791. • McCrimmon CM, King CE, Wang PT, Cramer SC, Nenadic Z, Do AH. Brain-controlled functional electrical stimulation therapy for gait rehabilitation after stroke: a safety study. Journal of neuroengineering and rehabilitation. 2015;12(1):57. • Do AH, Wang PT, King CE, Abiri A, Nenadic Z. Brain-computer interface controlled functional electrical stimulation system for ankle movement. J Neuroeng Rehabil. 2011;8:49. Available from: http://dx.doi.org/10.1186/1743-0003-8-49. • Do AH, Wang PT, King CE, Schombs A, Cramer SC, Nenadic Z. Brain-computer interface controlled functional electrical stimulation device for foot drop due to stroke. In: Proc 34th Ann Int Conf IEEE Eng Med Biol Soc; 2012. p. 6414–6417. • McCrimmon C, Fu J, Wang M, Lopes LS, Wang P, Karimi-Bidhendi A, et al. Performance Assessment of a Custom, Portable and Low-Cost Brain-Computer Interface Platform. IEEE Transactions on Biomedical Engineering. 2017. • McCrimmon CM, Wang PT, Nenadic Z, Do AH. BCI-Based Neuroprostheses and Physiotherapies for Stroke Motor Rehabilitation. In: Neurorehabilitation Technology. Springer; 2016. p. 617–627.

Subject Population(s) (Individuals/Records/Biospecimens)

Check all subject populations/data sources that apply to the research:

Adults Competent to Provide Informed Consent

Maximum and Expected Number of Persons/Records/Biospecimens to be Enrolled

1. Click "Add Line" button above Enrollment Table to add a Category/Group
    a. To change visibility of columns, click "Columns" button above Enrollment Table and select which Column rows to view.
2. Specify the maximum and expected numbers of individual-level information and/or biospecimens to be accessed/analyzed within each Category/Group

Category/Group

Adults (Aim 1 and 2)

Age Range

18-80

Maximum Number of Subjects, Subjects to be Consented or Reviewed/Collected

200

Number Expected to Complete the Study or Needed to Address the Research Question

80

Category/Group

Adults (Aim 3)

Age Range

18-80

Maximum Number of Subjects, Subjects to be Consented or Reviewed/Collected

40

Number Expected to Complete the Study or Needed to Address the Research Question

20

Will this study only take place at UCI and does not involve other sites?

Yes

Eligibility Factors (Inclusion/Exclusion Criteria)

1. Click "Add Line" button above Eligibility Factors Table to add a inclusion/exclusion criteria
    a. To change visibility of columns, click "Columns" button above Eligibility Factors Chart and select which Column rows to view.
2. Identify the factors for limited eligibility and provide a scientific rationale. Include additional rows for factors, as needed.

Category/Group Eligibility

Adults - all groups

Inclusion Criteria

1. Age18-80 years inclusively at time of consent; 2. Radiologically confirmed stroke, ischemic or intracerebral hemorrhage (ICH) in etiology, with day of onset at least 26 weeks prior to day of randomization 3. Gait velocity<0.8 m/s at screening and baseline visits. 4. Foot-drop in affected limb as defined by dorsiflexion active range of motion (AROM) via goniometry in seated position foot dangling is less than passive range of motion and less than 15 degrees. 5. Plantarflexors spasticity<3 on modified Ashworth Scale; 6. Can walk >10 m (with or without ankle foot orthosis (AFO), and cane or walker permitted) at a supervised level; 7. Can tolerate FES with pain no more than 4 on pain analog scale and has adequate muscle response of dorsiflexion ≥10 degrees; 8. Passive Range of Motion at least 0 degrees ankle dorsiflexion in subtalar neutral or with FES

Exclusion Criteria

Exclusion Criteria: 1. A major, active, coexistent medical, neurological (apart from stroke) or psychiatric disease (apart from stroke), including alcoholism or dementia, orthopedic injuries, that substantially affects gait. **Because old orthopedic injuries may or may not affect gait, at the discretion of the site's study PI, exclusion criterion #2 related to orthopedic injuries can be waived if the joint/muscles are back to normal motor and range of motion function. 2. A major medical disorder that substantially reduces the likelihood that a subject will be able to comply with all study procedures or safely complete study procedures. This includes, but not limited to documented serious cardiac conditions, serious pulmonary conditions, legal blindness, end stage renal or liver disease, pulmonary embolism or deep venous thrombosis. 3. Resting systolic blood pressure above 170, diastolic blood pressure above 100 at screening and baseline evaluations 4. Implanted electronic device (e.g. pacemaker) or skull metallic implants (e.g. cranioplasty plate covering the leg motor area) with which study research procedures are contraindicated or incompatible. 5. Deficits in communication that interfere with reasonable study participation: language or attention impairment (score>1 on NIH Stroke Scale items 9 and 11, respectively) 6. Significant cognitive impairment, defined as Montreal Cognitive Assessment score < 22 (For those with aphasia: **Because Montreal Cognitive Assessment scores may be difficult to interpret for patients with aphasia, at the discretion of the site's study PI, exclusion criterion #5 (“MoCA score cannot be <22”) can be waived) 7. A new symptomatic stroke occurs apart from the index stroke during the screening process and prior to randomization 8. Life expectancy < 6 months 9. Skin breakdown over electrical stimulation sites; 10. Received chemical denervation (eg Botox) to legs in the preceding 6 months, or expectation that chemical denervation will be administered to the leg prior to expected completion of the study 11. Unable or unwilling to perform study procedures/therapy, or expectation of non-compliance with study procedures/therapy 12. Pregnancy; 13. Significant pain (visual analog scale >4), chest pain, or shortness of breath with walking. 14. Receiving any outside concurrent physical therapy involving the lower extremities after enrollment in the study up to 1 month post treatment 15. Any general medical condition and psychosocial situation that substantially interferes with reasonable participate in study appointments 16. Non-English

speaking, such that subject does not speak sufficient English to comply with study procedures 17. Concurrent enrollment in another investigational interventional study 18. Severe depression, defined as Geriatric Depression Scale Score >11: **Because Geriatric Depression scale scores may be difficult to interpret for some patients, at the discretion of the site's study PI, exclusion criterion #17 (“Geriatric Depression score cannot be >11”) can be waived) 19. Concurrent use of FES orthosis for gait. 20. A new symptomatic stroke occurs apart from the index stroke during the screening process and prior to randomization If TMS Eligible (note that potential subjects who do not qualify for TMS will not be excluded from the main study, they will only be excluded from undergoing TMS procedures): 21. TMS: Metallic hardware on the scalp (e.g. vascular clips or cranioplasty mesh) 22. TMS: Implanted medication pumps, intracardiac line, or central venous catheter 23. TMS: History of cortical stroke or other cortical lesion such as brain tumor 24. TMS: Prior diagnosis of seizure or epilepsy 25. TMS: Any electrical, mechanical, or magnetic implants 26. TMS: History of neurosurgery 27. TMS: uncontrolled Migraine headaches 28. TMS: Any current medications that affect seizure threshold such as tricyclic antidepressants and neuroleptics 29. TMS: Unstable medical conditions

Is eligibility based on age, gender, pregnancy/childbearing potential, social/ethnic group, or language spoken (e.g., English Speakers only)?

Yes

Limited Eligibility Factors (Special Populations)

1. Click "Add Line" button above Limited Eligibility Factors Table to add a special population
    a. To change visibility of columns, click "Columns" button above Limited Eligibility Factors Table and select which Column rows to view.
2. Identify the special populations and provide a scientific rationale. Add additional rows, as needed.

Eligibility Limited to the Following Factors

Age

Specify the rationale for this group:
Only patients age 18-80 will be recruited. Children and minors have brains that are still developing and will add additional unknown/variability to the study. Adults over 80 years of age will be excluded because the aging process produces deteriorations in motor control and motor learning, and thus age is a confounding factor for identifying changes in motor ability due to BCI training. English speaking only: The program for the BCI system is only written in English. When other languages are available, the study can be expanded.

Eligibility Limited to the Following Factors
Language Spoken (e.g., English speakers only)

Specify the rationale for this group:
The program for the BCI system is only written in English

Eligibility Limited to the Following Factors
Language Spoken (e.g., English speakers only)

Specify the rationale for this group:
non-English speakers are excluded because the program for the BCI system is only written in English

Pre-Screening and Determining Eligibility without Informed Consent

Will Identifiable information be obtained for the purpose of screening, recruiting, or determining eligibility of prospective subjects?
Yes

The 2018 Common Rule allows for Pre-Screening activities (i.e., determining if potential subjects may be eligible to participate in research) performed without the written informed consent of the prospective subject or legally authorized representative (LAR). This means that the IRB does not need to grant a waiver of informed consent.

Provide a complete list of the data points, variables, and/or information that will be collected during Pre-Screening (i.e. data abstraction form):

Or specify variables or information required for Pre-Screening:
radiologically confirm stroke through review of imaging, time of stroke (greater than 6 months); age; presence of gait impairment due to stroke

Check all the Pre-Screening activities that apply:
Study team will screen medical records to determine subject eligibility

Select Medical Record Source (check all that apply):
Other medical record source
Study team will access their own UCI patients' records and abstract data directly from those records
Study team will request Non-UCI Health records and abstract data directly from those records

Other Medical Record Source

Explain 'Other' medical record source:
The study team will request specific patient information/data from UCIMC Health Information Management Services.

The Study Team Will Request Non-UCI Health Records and Abstract Data Directly from those Records

Enter the name(s) of Non-UCI Entity/Entities:
other medical institutions where study participants have medical records to be reviewed after subjects sign the HIPAA Authorization

How will the study team request Non-UCI Health records and abstract data directly from those records?

Specify the non-UCI Health records that will be screened: History and physical notes pertaining to stroke admission, neurology consult notes, rehabilitation service notes, and MRI brain images Explain how the study team has access to this clinical data: Potential subjects who are interested who have passed initial screening and agree to sign HIPAA waiver for release of information. Our research team will either screen copies of the records provided to us by the potential subject or will contact the appropriate medical institution to request a copy of the above record types for review. Subjects will sign the HIPAA non-UCI provider form and only after it's signed will non-UCI records be released to study team.

Will the study team screen stored identifiable biospecimens?

No

Will the study team contact subjects for eligibility or recruitment purposes?

No

Recruitment Methods

Will this study involve NO direct contact with participants (i.e., passive observation of public behavior)?

No

Indicate all methods that will be used to recruit subjects for this study:

Recruitment Method

Flyers/Brochures

Specify Where Posted

Approved recruitment materials may be posted in local newspapers, on the American Heart Association/American Stroke association and local stroke support group websites. Recruitment materials may also be posted on social media platforms such as Facebook, Twitter and Reddit. A Facebook page for the study was created at: https://www.facebook.com/legtherapystudy/

Type of Space

Private (i.e., site/media that allows control of access to content)

Confirm that applicable consent documents will include reference to the use of SONA

Confirm that the ClinicalTrials.gov statement is in all applicable consent documents

Confirm that the study from the Center for Clinical Research (CCR) Find a Trial web page is registered on ClinicalTrials.gov

Specify how contact information will be obtained:

Specify how these individuals granted permission and enter HS#:

Examples:

- Individuals who are economically or educationally disadvantaged
- Individuals that have impaired decision-making capacity
- Physician's own inpatients and/or outpatients
- Students (undergraduate, graduate, and medical students)
- Employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.)

IRB requires that:

1. Subjects will be approached with an emphasis that participation is voluntary; and
2. Subject will be informed in a caring manner that no matter their decision, it will NOT affect:
    a. Their relationship with UCI
    b. How their doctor cares for them as a patient or their care at UC Health in general and/or
    c. How their instructor grades their participation in the course; and
3. A statement attesting the information above in item b will be included in applicable recruitment and/or consent documents.

Confirm that colleagues may provide a copy of the consent and other UCI IRB approved materials but do not obtain subjects' consent for the research or act as representatives of the investigators

Confirm that:

1. The recruitment letter to be signed by the treating physician will be submitted in the Attachments Section
2. Colleagues do not obtain subjects' consent for the research or act as representatives of the investigators

Specify 'Other' recruitment methods:

Specify the precautions taken to avoid compromised objectivity:

Recruitment Method

Online/Social Media

Specify Where Posted

Completely passive approach will be utilized where potential participants are not presented with the info about study participation directly, whomever is interest will contact study team first if interested, and no contact with be made nor initiated from study team (e.g. general posting of study not linking to each individual's account, and where consideration for method of approach has provisions in place to ensure patient/physician confidentiality and/or subject privacy are not compromised).

Type of Space

Private (i.e., site/media that allows control of access to content)

Confirm that applicable consent documents will include reference to the use of SONA

Confirm that the ClinicalTrials.gov statement is in all applicable consent documents

Confirm that the study from the Center for Clinical Research (CCR) Find a Trial web page is registered on ClinicalTrials.gov

Specify how contact information will be obtained:

Specify how these individuals granted permission and enter HS#:

Examples:

- Individuals who are economically or educationally disadvantaged
- Individuals that have impaired decision-making capacity
- Physician's own inpatients and/or outpatients
- Students (undergraduate, graduate, and medical students)
- Employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.)

IRB requires that:

1. Subjects will be approached with an emphasis that participation is voluntary; and
2. Subject will be informed in a caring manner that no matter their decision, it will NOT affect:
    a. Their relationship with UCI
    b. How their doctor cares for them as a patient or their care at UC Health in general and/or
    c. How their instructor grades their participation in the course; and
3. A statement attesting the information above in item b will be included in applicable recruitment and/or consent documents.

Confirm that colleagues may provide a copy of the consent and other UCI IRB approved materials but do not obtain subjects' consent for the research or act as representatives of the investigators

Confirm that:

1. The recruitment letter to be signed by the treating physician will be submitted in the Attachments Section
2. Colleagues do not obtain subjects' consent for the research or act as representatives of the investigators

Specify 'Other' recruitment methods:

Specify the precautions taken to avoid compromised objectivity:

Recruitment Method

Clinicaltrials.gov

Specify Where Posted

Type of Space

Confirm that applicable consent documents will include reference to the use of SONA

Confirm that the ClinicalTrials.gov statement is in all applicable consent documents

Confirm that the study from the Center for Clinical Research (CCR) Find a Trial web page is registered on ClinicalTrials.gov

Specify how contact information will be obtained:

Specify how these individuals granted permission and enter HS#:

Examples:

- Individuals who are economically or educationally disadvantaged
- Individuals that have impaired decision-making capacity
- Physician's own inpatients and/or outpatients
- Students (undergraduate, graduate, and medical students)
- Employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.)

IRB requires that:

1. Subjects will be approached with an emphasis that participation is voluntary; and
2. Subject will be informed in a caring manner that no matter their decision, it will NOT affect:
    a. Their relationship with UCI
    b. How their doctor cares for them as a patient or their care at UC Health in general and/or
    c. How their instructor grades their participation in the course; and
3. A statement attesting the information above in item b will be included in applicable recruitment and/or consent documents.

Confirm that colleagues may provide a copy of the consent and other UCI IRB approved materials but do not obtain subjects' consent for the research or act as representatives of the investigators

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1. The recruitment letter to be signed by the treating physician will be submitted in the Attachments Section
2. Colleagues do not obtain subjects' consent for the research or act as representatives of the investigators

Specify 'Other' recruitment methods:

Specify the precautions taken to avoid compromised objectivity:

Recruitment Method

Other recruitment methods

Specify Where Posted

Type of Space

Confirm that applicable consent documents will include reference to the use of SONA

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Examples:

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- Individuals that have impaired decision-making capacity
- Physician's own inpatients and/or outpatients
- Students (undergraduate, graduate, and medical students)
- Employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.)

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    a. Their relationship with UCI
    b. How their doctor cares for them as a patient or their care at UC Health in general and/or
    c. How their instructor grades their participation in the course; and
3. A statement attesting the information above in item b will be included in applicable recruitment and/or consent documents.

Confirm that colleagues may provide a copy of the consent and other UCI IRB approved materials but do not obtain subjects' consent for the research or act as representatives of the investigators

Confirm that:

1. The recruitment letter to be signed by the treating physician will be submitted in the Attachments Section
2. Colleagues do not obtain subjects' consent for the research or act as representatives of the investigators

Specify 'Other' recruitment methods:

The study will be listed on the UC Irvine Health Clinical Trials web page.

Specify the precautions taken to avoid compromised objectivity:

Recruitment Method

Study team will approach subjects who are vulnerable to undue influence or coercion (i.e. students, employees and patients)

Specify Where Posted

Type of Space

Confirm that applicable consent documents will include reference to the use of SONA

Confirm that the ClinicalTrials.gov statement is in all applicable consent documents

Confirm that the study from the Center for Clinical Research (CCR) Find a Trial web page is registered on ClinicalTrials.gov

Specify how contact information will be obtained:

Specify how these individuals granted permission and enter HS#:

Examples:

- Individuals who are economically or educationally disadvantaged
- Individuals that have impaired decision-making capacity
- Physician's own inpatients and/or outpatients
- Students (undergraduate, graduate, and medical students)
- Employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.)

IRB requires that:

1. Subjects will be approached with an emphasis that participation is voluntary; and
2. Subject will be informed in a caring manner that no matter their decision, it will NOT affect:
    a. Their relationship with UCI
    b. How their doctor cares for them as a patient or their care at UC Health in general and/or
    c. How their instructor grades their participation in the course; and
3. A statement attesting the information above in item b will be included in applicable recruitment and/or consent documents.

Confirm that colleagues may provide a copy of the consent and other UCI IRB approved materials but do not obtain subjects' consent for the research or act as representatives of the investigators

Confirm that:

1. The recruitment letter to be signed by the treating physician will be submitted in the Attachments Section
2. Colleagues do not obtain subjects' consent for the research or act as representatives of the investigators

Specify 'Other' recruitment methods:

Specify the precautions taken to avoid compromised objectivity:

When enrolling researchers' own patients: Subjects will be approached with an emphasis that participation is voluntary; and Subject will be informed in a caring manner that no matter their decision, it will NOT affect: Their relationship with UCI How their doctor cares for them as a patient or their care at UC Health

Recruitment Method

Colleagues provide subjects with information about the research and how to contact investigators

Specify Where Posted

Type of Space

Confirm that applicable consent documents will include reference to the use of SONA

Confirm that the ClinicalTrials.gov statement is in all applicable consent documents

Confirm that the study from the Center for Clinical Research (CCR) Find a Trial web page is registered on ClinicalTrials.gov

Specify how contact information will be obtained:

Specify how these individuals granted permission and enter HS#:

Examples:

- Individuals who are economically or educationally disadvantaged
- Individuals that have impaired decision-making capacity
- Physician's own inpatients and/or outpatients
- Students (undergraduate, graduate, and medical students)
- Employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.)

IRB requires that:

1. Subjects will be approached with an emphasis that participation is voluntary; and
2. Subject will be informed in a caring manner that no matter their decision, it will NOT affect:
    a. Their relationship with UCI
    b. How their doctor cares for them as a patient or their care at UC Health in general and/or
    c. How their instructor grades their participation in the course; and
3. A statement attesting the information above in item b will be included in applicable recruitment and/or consent documents.

Confirm that colleagues may provide a copy of the consent and other UCI IRB approved materials but do not obtain subjects' consent for the research or act as representatives of the investigators

Confirm that:

1. The recruitment letter to be signed by the treating physician will be submitted in the Attachments Section
2. Colleagues do not obtain subjects' consent for the research or act as representatives of the investigators

Specify 'Other' recruitment methods:

Specify the precautions taken to avoid compromised objectivity:

Recruitment Method

Other recruitment methods

Specify Where Posted

Type of Space

Confirm that applicable consent documents will include reference to the use of SONA

Confirm that the ClinicalTrials.gov statement is in all applicable consent documents

Confirm that the study from the Center for Clinical Research (CCR) Find a Trial web page is registered on ClinicalTrials.gov

Specify how contact information will be obtained:

Specify how these individuals granted permission and enter HS#:

Examples:

- Individuals who are economically or educationally disadvantaged
- Individuals that have impaired decision-making capacity
- Physician's own inpatients and/or outpatients
- Students (undergraduate, graduate, and medical students)
- Employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.)

IRB requires that:

1. Subjects will be approached with an emphasis that participation is voluntary; and
2. Subject will be informed in a caring manner that no matter their decision, it will NOT affect:
    a. Their relationship with UCI
    b. How their doctor cares for them as a patient or their care at UC Health in general and/or
    c. How their instructor grades their participation in the course; and
3. A statement attesting the information above in item b will be included in applicable recruitment and/or consent documents.

Confirm that colleagues may provide a copy of the consent and other UCI IRB approved materials but do not obtain subjects' consent for the research or act as representatives of the investigators

Confirm that:

1. The recruitment letter to be signed by the treating physician will be submitted in the Attachments Section
2. Colleagues do not obtain subjects' consent for the research or act as representatives of the investigators

Specify 'Other' recruitment methods:

mailings to local neurologists, rehab doctors, hospitals, and other health professionals.

Specify the precautions taken to avoid compromised objectivity:

Informed Consent Process

Does this study involve the creation, use, or disclosure of Protected Health Information (PHI)?

Yes

Methods of Health Insurance Portability and Accountability Act (HIPAA) Authorization

Identify the HIPAA authorization process (Check all that apply):

Partial waiver of HIPAA authorization for screening/recruitment purposes only. Signed authorization obtained prior to further access to PHI

Signed HIPAA authorization obtained

Methods of Informed Consent

Identify the consent or assent process as applicable for each participant population (check all that apply):

Paper-based signed informed consent/assent

Paper-based Signed Informed Consent

Indicate the paper-based signed informed consent/assent (check all that apply):

Signed Informed Consent

REQUIRED! Submit the Adult Consent Form, Child Assent Form and/or Parental Permission Form in the Attachments Section.

Circumstances of Consent

Indicate the location where the consent process will take place (**check all that apply**):

Private room

Specify how the research team will assure that subjects, their parents, or their legally authorized representative (LAR) have sufficient time to consider whether to participate in the research:

Subjects or their LAR will be allowed to take home the unsigned consent form for review prior to signing it

---

This study does NOT include Non-English Speaking Participants. Scientific justification/rationale is required in the Eligibility Criteria Section for Subject Populations.

Waiver of HIPAA Authorization

You requested a Partial Waiver of HIPAA Authorization

When a partial waiver is requested, the Lead Researcher is requesting the HIPAA research authorization be waived for a portion of the study, such as a waiver for subject identification or recruitment purposes.

Please specify for what purpose the partial waiver is requested:

HIPAA waiver is needed to access medical records of UCI stroke patients for study eligibility purposes.

Justification for a Waiver of HIPAA Authorization

Does the use or disclosure of personal health information involve more than minimal risk?

No

Would the granting of the waiver adversely affect privacy rights and welfare of the individuals whose records will be used or disclosed?

No

Explain (justify) the answer:

Stroke subject medical records would be reviewed exclusively for study eligibility information.

Could the research practicably be conducted without a waiver of HIPAA authorization?

No

Explain the answer:

Eligibility requirements are specific and can only be identified via a review of stroke patient medical records.

Could the research practicably be conducted without access to, use or disclosure of the personal identifiers listed in the PHI question?

No

Explain the answer:

Personal identifiers must be attained by study personnel in order to contact potential study subjects for recruitment.

Are the privacy risks reasonable relative to the anticipated benefits of the research?
Yes

Describe the risk/benefit analysis performed to explain the answer above:
Review of medical records will allow stroke patients the opportunity to be part of a study where there is a possibility that they will experience improved walking ability, however this benefit is not guaranteed.

Describe the plan to protect the personal identifiers from improper use and disclosure (i.e., describe data security methods):
All information attained from medical records will be stored in a password protected excel document stored on password protected computers in locked UCI research offices.

Describe the plan to destroy the personal identifiers at the earliest opportunity, or provide a health or research justification for retaining the identifiers:
All personal identifiers attained for subjects who do not meet eligibility requirements will be destroyed as soon as ineligibility is determined.

Describe how potential subjects will be identified:
Potential subjects will be identified via by examining the neurology and acute rehabilitation unit inpatient lists.

Research Procedures

Check all boxes that apply to the research:
Audio, Video, Digital or Image Recording and/or Photography for Collection of Research Data
Clinical Investigation involving an Investigational Device
Other Non-invasive Physical Measurements (e.g., ECG, EEG, moderate exercise, muscular strength testing, body composition assessment)

Will deception or incomplete disclosure be involved in the research?
No

Study Design

Include an explanation of the study design (e.g., randomized placebo-controlled, cross-over, cross-sectional, longitudinal, etc.) and, if appropriate, describe stratification/ randomization/blinding scheme:

Aim 1 is a parallel, 2-arm randomized controlled Phase 2 clinical trial. Aim 3 is a randomized, 2-arm randomized controlled study (not a clinical trial). They will produce the following study groups 1. Aim 1 – randomization 1:1 between 2 groups as follows: a. Group 1 (40 subjects): undergoing multiple sessions of 1 hour BCI-FES therapy followed by 1 hour of conventional physical therapy b. Group 2(40 subjects): undergoing multiple sessions of 2 hour conventional physical therapy sessions 2. Aim 3 – randomization 1:1 between 2 groups as follows: a. Group 3 (10 subjects): BCI-FES therapy (no conventional physical therapy) b. Group 4 (10 subjects): BCI-robotic orthosis therapy (no conventional physical therapy) BCI-FES therapy: Group 1 subjects will undergo placement of a 4-channel EEG cap using standard technique (Cz, Cpz, C1, C2) and be connected to our custom BCI system (from Study 1a). Note that based on Study 3, this electrode selection will likely capture brain areas subserving dorsiflexion for all stroke subjects. Subjects will provide 5 min of training EEG data as they engage in alternating epochs of idling and attempted foot dorsiflexion (of the paretic side). The automated software will analyze the data to generate and calibrate a BCI decoder (additional 5-10 mins). In the online phase (involves actively operating the BCI system in real-time), the subjects will perform 20-25 BCI-FES runs (total of 1 hour). In each run, subjects will follow 10 alternating epochs of 10-s long idling/dorsiflexion textual cues, and respond by either idling or attempting dorsiflexion to elicit BCI-FES mediated contractions of the TA muscle. A total of 12 sessions will be performed at a rate of 3x/week (over 4 weeks). Each BCI-FES therapy session will be followed by 1 hour of conventional physiotherapy as described below. Conventional Physical Therapy: This will consist of a standardized regimen of activities typical of conventional post-stroke gait therapy, including passive/active range of motion exercises (to reduce/prevent excessive plantarflexor contractures), lower-extremity muscle strengthening, and a progression from treadmill to overground walking exercises. A total of 12 sessions will be performed at 3x/week. For Group 1, conventional physiotherapy will immediately follow each BCI-FES session and last for 1 hour. In the dose-matched control group (Group 2), it will be 2 hours/session. Subjects will not be allowed to undergo outside physiotherapy for the entire

study. A commercial company will be used to assign patients a 30 minute home exercise program to be completed 4 times a week with compliance assessed via non-invasive sensors. For those without a mobile device, a pen and paper version of the home exercise program will also be available. Aim 3: The aim is designed as a randomized controlled study with two arms: BCI-FES dorsiflexion therapy and BCI-robotic orthosis therapy. A total of 20 subjects will be recruited and randomized with 1:1 ratio into the two arms. The primary outcome is gait velocity, and the secondary outcomes are ankle torque and active range of motion. The main interest is to evaluate if the correlation between M1→EMG, w, (normalized range: 0-1), and gait velocity is different between the two study groups averaged over time after treatment, adjusted for baseline outcome measure. For example, with outcome gait velocity, the analysis will be based on a regression model with group, we, and their interaction, adjusted for baseline gait velocity. The relationship between both w with secondary outcomes will be similarly analyzed. TR-NIRS parameters will be measured at the TA muscle of stroke patients while they attempt dorsiflexion while seated with the tibia perpendicular to the ground. Measurements pertaining to oxygen metabolism at the TA muscle will be acquired by placing the source and detector fibers on the skin surface positioned over the muscle (using the adhesive pads). This setup allows for the collection of metabolic data in real time while either the BCI-FES or BCI-robotic orthosis systems are being used.

Provide precise definitions of the study endpoints and criteria for evaluation; if the primary outcomes are derived from several measurements (i.e., composite variables) or if endpoints are based composite variables, then describe precisely how the composite variables are derived:

Aim 1: The primary outcome measure will be gait velocity, which is directly linked to disability and social re-integration after stroke. Gait velocity will be assessed by measuring the time to traverse the middle 6 m of a 10-m walkway (5 repetitions/assessment). Secondary outcomes include: 1. Gait endurance: The distance walked over 6 minutes. 2. Fall Frequency: Number of falls experienced weekly. 3. Leg Motor Fugl-Meyer (FM) Score: Assessed according to the FM rating system. 4. Dorsiflexion Active Range of Motion (AROM) and torque: The paretic foot will be placed in an articulated brace which maintains the ankle at neutral during idling, while fixing the tibia perpendicular to the ground and the femur horizontal to the ground. The brace will be instrumented with an electro-goniometer and torque meter to automatically measure the maximum dorsiflexion AROM and torque (over 3 trials). 5. EEG Map: Subjects will undergo 64-channel EEG recording as they engage in 100 alternating 10-s long epochs of idling and attempted dorsiflexion. The EEG ERD/ERS, defined as the drop/rise in alpha (8-12 Hz) and beta (13-30 Hz) band power during attempted dorsiflexion (compared to idling), will be calculated and averaged over all epochs and across all channels. A pre-intervention baseline for each outcome will first be established. Subsequently, measurements will be performed at 1 week intervals during the intervention phase (total of 3), immediately after the intervention phase, as well as 1 and 3 months after completion of interventions. The primary efficacy outcome and endpoint will be gait velocity immediately after the intervention phase. Aim 2 (subgroup analysis of Phase II clinical trial) Since stroke is a heterogeneous disease, responsiveness to rehabilitation therapy is not uniform across all subpopulations. Hence, it is important to ensure that any new therapy, e.g. BCI-FES therapy, is matched to subpopulations that will benefit the most. The following set of baseline characteristics will be assessed during the pre-intervention phase (Fig. 6, Phase 2) for Groups 1 and 2 to determine which features influence responsiveness to BCI-FES therapy: 1. Baseline gait velocity, dorsiflexion AROM and torque: Baseline gait velocity and dorsiflexion AROM and torque will be taken from Aim 1. 2. TA volitional electromyogram (EMG): TA EMG will be assessed by having subjects attempt dorsiflexion while seated with tibia perpendicular to ground. EMG will be acquired by a bioamplifier with surface electrodes placed over the TA muscle. Subjects will be categorized as either

having TA EMG or no response (no detectable EMG activity after 4 attempts). 3. EEG features: Movement induced EEG ERD/ERS and its spatial distribution in μ (8-12 Hz) and β (13-30 Hz) bands may change after stroke. Since BCI-FES therapy depends upon and possibly alters μ and β modulation, it is important to understand how the baseline ERD/ERS magnitude affects response to the therapy. EEG prior to the first BCI-FES session will be taken from Aim 1. 4. Nottingham Sensory Score: Baseline sensory impairment, as assessed by the Nottingham sensory system, can help determine if BCI-FES therapy can circumvent this requirement or not. Note that subjects will be informed that they are to refrain from starting any additional new physical therapies or other studies in stroke recovery for the entire duration of the study (including post-therapy visits). Subjects will be informed that those who become involved in outside therapy will be removed from the study as this may confound the scientific results. Aim 3 (Mechanism study, not a clinical trial): In order to elucidate the plasticity mechanism underlying BCI-FES therapy, it is necessary to compare BCI-FES therapy to a control. Hence, two new groups of chronic stroke subjects with foot-drop will be recruited (10 subjects each, same selection criteria as in Aim 1). The first group (Group 3), will undergo BCI-FES therapy as in Aim 1 (no concurrent physiotherapy). The second group (Group 4), will undergo BCI-robotic orthosis therapy. This comparison will allow us to determine if the mechanism of BCI-FES therapy is via enhanced sensory feedback, or via co-incident activation of upper and lower motor neurons. BCI-robotic orthosis therapy is similar to BCI-FES therapy, except that the FES system is replaced by a robotic orthosis that dorsiflexes the foot when attempted dorsiflexion is detected from EEG. The use of a BCI-robotic allows us to test if sensory feedback is the primary driver of the neurological improvements or if co-incident firing between the brain motor cortex and muscles is the primary driver. It should be noted that BCI-FES and BCI-robot therapies both provide sensory feedback, but only BCI-FES provides co-incident firing between the brain motor cortex and the muscles. The primary outcome examined here will also be gait velocity. Other secondary outcomes include gait endurance and TA volitional EMG, as described above. Assessments are on done on the same schedule as in Aim 1. This device will be used because, unlike EMG, NIRS systems are optically based. This allows for continuous monitoring at the muscle while the FES system is in use. EMG systems do not allow for continuous measurements when using FES, given that EMG systems measure electrical activity at the muscle that cannot be separated from the electrical activity of the FES system. TR-NIRS data will

provide insight into the metabolic changes at the TA muscle that can be compared between patients in the BCI-FES and BCI-robotic orthosis groups. This data will not only aid the stroke research community but will also aid the rehabilitation field in understanding healing dynamics post injury. The coherence between the Cz EEG electrode and the TA EMG will be calculated, known as w. The correlation between gait velocity and w will be calculated across the entire duration of study for all subjects. This will be repeated for both BCI-FES groups and BCI-robotic orthosis groups. Comparing the correlation between these 2 groups can provide insight into which of the above mechanisms is primarily driving plasticity.

Statistical Considerations

Is a statistical analysis plan appropriate for this qualitative study design?

Yes

Describe the statistical methods for the stated specific aims and hypotheses. Your analysis plans should match the stated study specific aims and hypotheses:

Aim 1: The study design is a parallel randomized controlled trial with two arms: BCI-FES dorsiflexion therapy and dose-matched conventional physical therapy. A total of 80 subjects (which includes 10% attrition) will be randomized with 1:1 ratio into the two study arms. The primary outcome is gait velocity and the secondary outcomes are gait endurance, fall frequency, leg motor FM score, and dorsiflexion AROM and torque. Outcomes measures will be evaluated at baseline, weekly during therapy, immediately post-intervention, and 1- month and 3-months post-therapy. The primary efficacy analysis (with intent-to-treat analysis with respect to treatment randomized) will be based on a linear mixed model (LMM) with gait velocity measured at baseline weeks 1-4 (time 0, 1, 2, 3, and 4) with time, treatment group and group by time interaction assess the difference in the rates of change (improvement) in gait velocity between treatment groups. Model estimation will be based on restricted maximum likelihood (REML) with unstructured covariance among repeated measurements over time. The LMM will also be applied to evaluate group difference for secondary outcomes and secondary endpoints at 1- and 3-months post-therapy. In order to determine if μ and β ERD/ERS significantly changes over the 4 weeks of therapy, the ERD and ERS magnitude will be calculated for each EEG channel across all attempted dorsiflexion epochs, and for each assessment. The Mann-Whitney U test will be used to determine if any significant changes in the magnitude of ERD/ERS at each assessment with respect to the baseline. Based on the findings, each subject will be categorized as demonstrating significant changes in ERD/ERS or not. Next, all subjects will also be categorized on whether they experienced a detectable increase in gait velocity (defined as an increase in gait velocity of >0.16 m/s with respect to baseline). A Chi-square test will be used to assess if there is a difference between the proportion of those with changes in ERD/ERS magnitude in those who had gait improvement within the BCI- FES therapy group. This will also be repeated for the control group. In addition, to determine if the presence of significant ERD/ERS changes was affected by group, the Chi-square test will be repeated by using BCI-FES group as the observation and the control group as the expected values. Aim 2: Data from Aim 1 will be used for analysis in this aim. The primary outcome is gait velocity immediately post-BCI-FES therapy, and the secondary outcomes are the same as in Aim 1. To test whether specific stroke features (e.g. baseline gait velocity, dorsiflexion AROM, etc.) modify response to treatment over

treatment duration, a LMM model with three-way interaction (group, time, modifying factor) will be used to test whether the slope of the three-factor interaction is zero (specific stroke feature does not modify response to treatment). Aim 3: The aim is designed as a randomized controlled study with two arms: BCI-FES dorsiflexion therapy and BCI-robotic orthosis therapy. A total of 20 subjects will be recruited and randomized with 1:1 ratio into the two arms. The primary outcome is gait velocity, and the secondary outcomes are ankle torque and active range of motion. The main interest is to evaluate if the correlation between M1→EMG, w, (normalized range: 0-1), and gait velocity is different between the two study groups averaged over time after treatment, adjusted for baseline outcome measure. For example, with outcome gait velocity, the analysis will be based on a regression model with group, we, and their interaction, adjusted for baseline gait velocity. The relationship between both w with secondary outcomes will be similarly analyzed.

Describe the statistical method(s) that will be used to analyze the primary outcome(s) or endpoints:

The primary statistical methods for primary outcome, gait velocity, is already described in Aim 1 above.

If appropriate describe secondary or post hoc analyses of primary outcome(s) or other exploratory analysis and if necessary, provide a breakdown of the methods used per outcome or endpoint:

The statistical method for secondary outcome measures is similar to the primary outcome, and is already described in Aim 1 and 2 above.

Sample Size Determination: **Explain how the overall target sample size was determined** (e.g., power analysis; precision estimation), **providing justification of the effect size for the primary outcome based on preliminary data, current knowledge/literature and/or cost consideration; if appropriate, provide sample size justification for secondary outcomes. Power analysis should (at least) match the primary outcome/endpoint:**

Power Analysis: For Aims 1 and 2, the power analysis was based on a LMM with two treatment groups and 5 repeated measures (baseline and after weeks 1-4) with a significance level of 0.05. Previous studies have examined the clinically meaningful gait improvement (minimal clinically important difference) of 0.16 m/s, including a multicenter randomized clinical trial that includes conventional physical therapy. Thus, to ensure clinically meaningful effect size, we assume conventional therapy will have an improvement of 0.25 m/s after 4 weeks of treatment. Data from prior studies as well as our own preliminary data (n=9) found that the between-subject variance in gait velocity of about 0.16 m/s and the within-subject correlation of about 0.95. Table 1 below shows the power to detect improvement of BCI-FES over conventional therapy of 30% - 40%. Thus, for the proposed study with n=80 patients (40 per arm) has 92% to 94% power to detect an effect size/improvement of 35% for various between-subject variance (0.15 m/s to 0.17 m/s) in determining treatment efficacy (Aim 1). We note that n=80 total has been intentionally inflated in order to accommodate the objectives of aim 2 to examine modifying factors, such as TA MEP (primary modifying factor), on treatment. That is, for n=30 per arm the power to determine efficacy (aim 1) is 85% for detecting an effect size/improvement of 35% (between-subject variance 0.16 m/s); thus, increasing to n=40 allows for detecting modifying factor on treatment (aim 2) when the interaction effect smaller (effect size 28% can be detected with 79% power). Table 1: Power to detect improvement in gait velocity due to BCI-FES over conventional therapy for n=80 with various between-subject variance (aim 1). Between-Subject Variance Effect Size (Improvement) 0.15 0.16 0.17 30% 87.3% 85.2 % 83.0% 35% 94.5% 93.5% 92.1% 40% 98.3% 97.7% 97.0% Aim 3: Total sample size of n=20 will have 82% power to detect an R-square of 0.16 (attributed to the effect of interest, e.g., w x group) adjusted for baseline measurement and main effects whose total contribution R-square is 0.5 (for 3 independent variables) in a multiple regression model.

Research Procedures

Provide a detailed chronological description of the clinical or treatment plan:

See attachment "ResearchProcsTable"

List all procedures involving the use and/or collection of photographs, or audio/video recording:

Photographs, video, audio may be taken for purposes of publication, and may include facial images. Any identifier, e.g. facial images, will be removed prior publication. Subject's participation in study does not depend on if they agree to have photos, videos, or audio taken.

Specify the total duration of a subject's participation in the study and clearly outline the duration of participation for each study visit and sub-study, as applicable:

Groups 1 and 2: Participation will last approximately 40 hours over 4 months and will include 17 visits. Groups 3 and 4: Participation will last approximately 30 hours over 4 months and will include 17 visits.

List data collection tools (e.g., measures, questionnaires, observational tool) below by clicking the 'Add Line' button. Include additional rows for study instruments, as needed:

The 'Columns' button allows you to display or hide columns in the Study Instrument List.

Name of Tool:

see ResearchProcsTable attachment to view the list of data collection instruments.

Is the data collection tool standardized or validated?

Yes

Please provide data collection tool citation:

Citations for validated assessments: 1)Fugl-Meyer: See J, Dodakian L, Chou C, Chan V, McKenzie A, Reinkensmeyer DJ, et al. A standardized approach to the fugl-meyer assessment and its implications for clinical trials. Neurorehabilitation and neural repair. 2013;27:732-741 2) NIH Stroke Scale: Schlegel D, Kolb SJ, Luciano JM, Tovar JM, Cucchiara BL, Liebeskind DS, Kasner SE. Utility of the NIH Stroke Scale as a predictor of hospital disposition. Stroke. 2003 Jan;34(1):134-7. 3) Modified Ashworth Scale: Lee G, An S, Lee Y, Lee D, Park DS. Predictive factors of hypertonia in the upper extremity of chronic stroke survivors. J Phys Ther Sci. 2015 Aug;27(8):2545-9. 4) Nottingham Sensory: Scalha TB, Miyasaki E, Lima NM, Borges G. Correlations between motor and sensory functions in upper limb chronic hemiparetics after stroke. Arq Neuropsiquiatr. 2011 Aug;69(4):624-9 5) Geriatric Depression Scale: Sivrioglu EY, Sivrioglu K, Ertan T, Ertan FS, Cankurtaran E, Aki O, Uluduz D, Ince B, Kirli S. Reliability and validity of the Geriatric Depression Scale in detection of poststroke minor depression. J Clin Exp Neuropsychol. 2009 Nov;31(8):999-1006 6) Modified Rankin Scale: Dennis M, Mead G, Doubal F, Graham C. Determining the modified Rankin score after stroke by postal and telephone questionnaires. Stroke. 2012 Mar;43(3):851-3. 7) Neuro QoL: Carlozzi NE, Tulsky DS, Kisala PA. Traumatic brain injury patient-reported outcome measure: identification of health-related quality-of-life issues relevant to individuals with traumatic brain injury. Arch Phys Med Rehabil. 2011 Oct;92(10 Suppl):S52-60 8) Gait Velocity: Tyson S, Connell L. The psychometric properties and clinical utility of measures of walking and mobility in neurological conditions: a systematic review. Clin Rehabil. 2009 Nov;23(11):1018-33. 9) Gait Endurance: Flansbjer UB, Holmbäck AM, Downham D, Patten C, Lexell J. Reliability of gait performance tests in men and women with hemiparesis after stroke. J Rehabil Med. 2005 Mar;37(2):75-82

Will this study require clinical items/ services from UC Irvine Health?

No

Does the research involve the use of identifiable private information?

Yes

Use of Identifiable Private Information as Part of the Main Study

Indicate the types/sources of identifiable private information (Check all that apply):

Identifiable photographs, images, or digital/audio/video recordings
Non-UCI Health Medical Records
UCI Health Medical Records

Identifiable Media

Specify identifiable photographs, images, or digital/audio/video recording source:

Photographs, video, audio may be taken for purposes of publication, and may include facial images. Any identifier, e.g. facial images, will be removed prior publication. Subject's participation in study does not depend on if they agree to have photos, videos, or audio taken.

Indicate whether the information was originally collected for research purposes:

Not originally collected for research

Explain how the information were originally collected (e.g., clinical care):

clinical care

Provide a complete list of the data points, variables, and/or information that will be collected (i.e. data abstraction form):

Or specify variables or information required here:

photo, video, audio

Specify the time-frame of the data to be accessed (e.g. January 2002 to 2024):

Any identifier, e.g. facial images, will be removed prior publication. Subject's participation in study does not depend on if they agree to have photos, videos, or audio taken. De-identified version will be maintained indefinitely in case of need for future research/publication

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This study will use medical records, indicate the source:

Study team will access their own UCI patients' records and abstract data directly from those records

Study team will request non-UCI Health records and abstract data directly from those records

UCI IRB approved protocol

The Study Team Will Request Non-UCI Health Records and Abstract Data Directly from those Records

Specify Non-UCI Entity:

History and physical notes pertaining to stroke admission, neurology consult notes, rehabilitation service notes, and MRI brain images

Explain how the study team will request non-UCI Health records and abstract data directly from those records:

Potential subjects who are interested who have passed initial screening and agree to sign HIPAA waiver for release of information. Our research team will either screen copies of the records provided to us by the potential subject or will contact the appropriate medical institution to request a copy of the above record types for review. Subjects will sign the HIPAA non-UCI provider form and only after it's signed will non-UCI records be released to study team.

UCI IRB Approved Protocol

Provide the HS number for the UCI IRB Approved Protocol study (enter multiple HS numbers if appropriate):

2004-3852, 2014-1607, 2017-4067

Does the research involve the use of identifiable biospecimens?

No

Sharing Results with Subjects

Will Individual results be shared with subjects?

No

Will overall study results will be shared with subjects?

The overall study results will be listed on Clinicaltrials.gov

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Medical Devices

Name of Device or Product

Brain-computer interface controlled functional electrical stimulation device

Device Manufacturer

UC Irvine

Description of the device:

The device consists of a circuit board which contains electronics necessary to acquire EEG signals, process the signals, and to control an electrical stimulator (TENS unit) to deliver FES to muscles. The device has a touch screen which is used by the operator to interact with it, and has connectors to attach an EEG cap. The entire circuit board is enclosed within a plastic case. A photo of the device is shown below (taken out of case).

Specify the proposed use of the device for this study:

The BCI-FES system will be used to deliver a form of BCI-based physiotherapy to stroke patients participating in the study. BCI-FES therapy: Group 1 subjects will undergo placement of a 4-channel EEG cap using standard technique (Cz, Cpz, C1, C2) and be connected to our custom BCI system (from Study 1a). Note that based on Study 3, this electrode selection will likely capture brain areas subserving dorsiflexion for all stroke subjects. Subjects will provide 5 min of training EEG data as they engage in alternating epochs of idling and attempted foot dorsiflexion (of the paretic side). The automated software will analyze the data to generate and calibrate a BCI decoder (additional 5-10 mins). In the online phase (involves actively operating the BCI system in real-time), the subjects will perform 20-25 BCI-FES runs (total of 1 hour). In each run, subjects will follow 10 alternating epochs of 10-s long idling/dorsiflexion textual cues, and respond by either idling or attempting dorsiflexion to elicit BCI-FES mediated contractions of the TA muscle. Further details of the procedure are provided in the study narrative.

Does this device have an Instructions for Use/User Manual/Product Brochure?

No

REQUIRED! **Submit the Instructions for Use, User Manual or Product Brochure in the Attachments Section**

Include information to describe how it works and the foreseeable risks associated with its use:

The BCI-FES system should not be considered a significant risk device. It is non-invasive, does not make any diagnoses, and does not sustain life. Its components, namely EEG and FES are both independently considered safe. Prior studies have demonstrated safe use of EEG and FES in combination. Risks and side effects related to the BCI-FES therapy include those which are: - Discomfort with wearing EEG electrodes (unlikely) - Increased falls (highly unlikely) - Fatigue (unlikely) - Skin breakdown due to electrical stimulation (highly unlikely)

Is the device a medical device?

Yes, this device is a medical device

If “no”, for minimal risk studies and the device is intended to be used in a clinical setting, provide justification for selecting “no”, citing any regulatory guidance as applicable:

Are you testing the safety and/or efficacy of this device?

Yes, we are assessing the safety and/or efficacy of this medical device; this is a clinical investigation

If “no”, for minimal risk research and if the device is the object of the investigation, provide justification for selecting “no”, citing any regulatory guidance as applicable:

Is the device approved for marketing in the United States?

No

How is the device approved in the United States?

REQUIRED! Submit FDA Documentation in the Attachments Section

Select one of the following:

Is the device authorized for use under an FDA Emergency Use Authorization (EUA)?

N/A

Is the device being used in this study according to its approved indication?

No, this device is not being used in this study according to its approved indication

Is the Device Exempt from the Investigational Device Regulations (21 CFR 812)?

No

Select the device exemption that meets one of the following categories:

Clarify how the device meets the category selected:

Is this device a Significant Risk (SR) device?

No, this device is not a significant risk device. This device is also not exempt; it is not a HUD/HDE

Has the investigator or sponsor of this research obtained an Investigational Device Exemption (IDE) from the FDA for the use of this device for this research?

REQUIRED! Submit the IDE Authorization Letter in the Attachments Section

IDE Number

Holder of the IDE (**check all that apply**):

Specify Lead Researcher:

Specify 'Other' IDE Holder:

Does the IDE allow billing of subjects?

Does the IDE cover a combination use (e.g., combination of an investigational drug and device)?

Specify the combination use:

Specify why an IDE has not been obtained yet:

Specify 'Other' reason:

Based on the criteria for a significant risk device listed in the link below, explain why the device as it is used in this study, qualifies as Non-Significant Risk (NSR) device:

According to the FDA criteria for significant risk determination (https://www.fda.gov/media/75459/download), the BCI-FES system is not a significant risk device as follows: -Is the device implanted?: No, this device is entirely non-invasive. -Does the device perform life sustaining functions?: No, this device does not perform any life sustaining functions -Is the device use of any substantial importance in diagnosis or treatment of disease?: No, this system does not perform any important diagnostic function. Although it is being tested for its potential efficacy in mitigating stroke related weakness and gait impairment, it does not pose any potential serious risk for health, safety, and welfare of a subject. The individual components, which include an EEG and an non-invasive FES device, are both independently non-invasive devices that are widely known to be safe. In fact, according to the FDA document above, both EEG and non-invasive FES is specifically listed as examples NSR devices. It is not expected that their combination should any potential for serious safety risk. -Otherwise being used in any way that presents a serious risk to health, safety, or welfare of a subject?: As indicated above, the individual components of the BCI-FES system include an EEG system and a non-invasive FES system. These devices are already examples of NSR devices as indicated by the FDA, and their use of them in combination is not expected to result in any serious safety risk. One example of a comparable combination use of EEG and FES is in non-invasive somatosensory evoked potentials, which is considered a safe, routine, outpatient procedure.

Has the FDA or another IRB determined the device to be non-significant risk as it is used in this study?

No

Indicate who will be responsible for the management of the device during the study:

Dr An Do and Dr Po Wang

Explain the plan to ensure that the investigational device is used only in accordance with the UCI IRB approved protocol:

Research team members will receive training on how the device is to be used, and will informed that it will only be used for the current study. A standard operating procedure will be provided to guide how the device should be operated each time it is used to deliver BCI-FES therapy.

Indicate who will have access to the device and how access will be controlled to secure the device (or device stock):

Dr An Do, Dr Po Wang and Dr Zoran Nenadic

Specify how records for control of the device (or device stock) will be recorded:

The sample Device Accountability Log on the HRPP website will be used

REQUIRED! Submit the Sponsor Device Log in the Attachment Section

Specify why no log will be used:

Indicate whether the investigational device is manufactured in a UCI facility:

Yes

Identify the lab and location:

UCI BCI Lab Gross Hall 1022

You have completed the form for this medical device. Click the 'Done' button. If you need to add more devices, click on the + Add Line button above the table to enter additional devices.

Name of Device or Product

Brain-computer interface controlled robotic orthosis

Device Manufacturer

UC Irvine

Description of the device:

The device consists of a circuit board which contains electronics necessary to acquire EEG signals, process the signals, and to control an robotic orthosis that moves the foot. The device has a touch screen which is used by the operator to interact with it, and has connectors to attach an EEG cap. The entire circuit board is enclosed within a plastic case. A photo of the device is shown below (taken out of case).

Specify the proposed use of the device for this study:

The BCI-FES system will be used to deliver a form of BCI-based physiotherapy to stroke patients participating in the study. Robotic exoskeleton sensory task: The robotic exoskeleton (same as used in already part of the study for Group 3 and 4) will be used for a foot position matching task. The subject will bear one robotic exoskeleton placed on each foot for the sensory testing. The foot position will be randomly moved by the exoskeleton and the subject will indicate when the ankle positions overlap. This will be repeated for a total of 25 times. BCI-robotic orthosis therapy is similar to BCI-FES therapy, except that the FES system is replaced by a robotic orthosis that dorsiflexes the foot when attempted dorsiflexion is detected from EEG. The use of a BCI-robotic allows us to test if sensory feedback is the primary driver of the neurological improvements or if co-incident firing between the brain motor cortex and muscles is the primary driver. It should be noted that BCI-FES and BCI-robot therapies both provide sensory feedback, but only BCI-FES provides co-incident firing between the brain motor cortex and the muscles.

Does this device have an Instructions for Use/User Manual/Product Brochure?

No

REQUIRED! **Submit the Instructions for Use, User Manual or Product Brochure in the Attachments Section**

Include information to describe how it works and the foreseeable risks associated with its use:

Risks and side effects related to the BCI-Robot operation include those which are: - Discomfort with wearing EEG electrodes (unlikely) - Increased falls (highly unlikely) - Fatigue (unlikely)

Is the device a medical device?

Yes, this device is a medical device

If "no", for minimal risk studies and the device is intended to be used in a clinical setting, provide justification for selecting "no", citing any regulatory guidance as applicable:

Are you testing the safety and/or efficacy of this device?

Yes, we are assessing the safety and/or efficacy of this medical device; this is a clinical investigation

If "no", for minimal risk research and if the device is the object of the investigation, provide justification for selecting "no", citing any regulatory guidance as applicable:

Is the device approved for marketing in the United States?

No

How is the device approved in the United States?

REQUIRED! Submit FDA Documentation in the Attachments Section

Select one of the following:

Is the device authorized for use under an FDA Emergency Use Authorization (EUA)?

N/A

Is the device being used in this study according to its approved indication?

No, this device is not being used in this study according to its approved indication

Is the Device Exempt from the Investigational Device Regulations (21 CFR 812)?

No

Select the device exemption that meets one of the following categories:

Clarify how the device meets the category selected:

Is this device a Significant Risk (SR) device?

No, this device is not a significant risk device. This device is also not exempt; it is not a HUD/HDE

Has the investigator or sponsor of this research obtained an Investigational Device Exemption (IDE) from the FDA for the use of this device for this research?

REQUIRED! Submit the IDE Authorization Letter in the Attachments Section

IDE Number

Holder of the IDE (**check all that apply**):

Specify Lead Researcher:

Specify 'Other' IDE Holder:

Does the IDE allow billing of subjects?

Does the IDE cover a combination use (e.g., combination of an investigational drug and device)?

Specify the combination use:

Specify why an IDE has not been obtained yet:

Specify 'Other' reason:

Based on the criteria for a significant risk device listed in the link below, explain why the device as it is used in this study, qualifies as Non-Significant Risk (NSR) device:

According to the FDA criteria for significant risk determination (https://www.fda.gov/media/75459/download), the BCI-robotic exoskeleton system is not a significant risk device as follows: -Is the device implanted?: No, this device is entirely non-invasive. -Does the device perform life sustaining functions?: No, this device does not perform any life sustaining functions -Is the device use of any substantial importance in diagnosis or treatment of disease?: No, this system does not perform any important diagnostic function. In Aim 3 of this study, the BCI controlled robotic ankle exoskeleton is being used as a tool to elucidate the potential mechanism of how BCI systems may elicit neuroplasticity. It is not being used to provide treatment for stroke rehabilitation. -Otherwise being used in any way that presents a serious risk to health, safety, or welfare of a subject?: This device is a non-invasive, wearable exoskeleton that has the capacity to passively measure movement trajectories and also actively manipulate the user's ankle as controlled via a BCI. The exoskeleton itself is similar to a category of devices called powered exercise equipment, which is designated as an exempt category per the FDA. Our specific exoskeleton is a seated system which is calibrated to the user's range of motion, with emergency cut off buttons and extensive training and well documented protocol/manual. It can provide robotically assisted dorsiflexion movement to the subject upon their intent to dorsiflexion attempt, uses a low amount of torque, and only operates within the subjects available range of motion. As such, it is not expected to pose any serious risk of orthopedic injury or other safety/welfare concerns to the subjects.

Has the FDA or another IRB determined the device to be non-significant risk as it is used in this study?

No

Indicate who will be responsible for the management of the device during the study:

Dr. Do and Dr. Reinkensmeyer

Explain the plan to ensure that the investigational device is used only in accordance with the UCI IRB approved protocol:

Research team members will receive training on how the device is to be used, and will informed that it will only be used for the current study. A standard operating procedure will be provided to guide how the device should be operated each time it is used to deliver BCI-robotic orthosis therapy.

Indicate who will have access to the device and how access will be controlled to secure the device (or device stock):

Dr. Reinkensmeyer, Jill See, and Vicky Chan

Specify how records for control of the device (or device stock) will be recorded:

The sample Device Accountability Log on the HRPP website will be used

REQUIRED! Submit the Sponsor Device Log in the Attachment Section

Specify why no log will be used:

Indicate whether the investigational device is manufactured in a UCI facility:

Yes

Identify the lab and location:

Hewitt Hall Room 1341

You have completed the form for this medical device. Click the 'Done' button. If you need to add more devices, click on the + Add Line button above the table to enter additional devices.

Name of Device or Product

MP150 bioamplifier with EMG100 attachment

Device Manufacturer

Biopac

Description of the device:

This is a standard research bioamplifier system that is used to record electromyogram or other peripheral nerve activity

Specify the proposed use of the device for this study:

This will be used to record the motor evoked potential from the tibialis anterior muscle, which is stimulated by the transcranial magnetic stimulation delivered to the brain. Manual links: https://www.biopac.com/wp-content/uploads/MP150-Systems.pdf EMG100C attachment: https://www.biopac.com/product/electromyogram-amplifier/

Does this device have an Instructions for Use/User Manual/Product Brochure?

Yes

REQUIRED! Submit the Instructions for Use, User Manual or Product Brochure in the Attachments Section

Include information to describe how it works and the foreseeable risks associated with its use:

Is the device a medical device?

Yes, this device is a medical device

If "no", for minimal risk studies and the device is intended to be used in a clinical setting, provide justification for selecting "no", citing any regulatory guidance as applicable:

Are you testing the safety and/or efficacy of this device?

No, the safety and/or efficacy of this medical device is not being assessed

If "no", for minimal risk research and if the device is the object of the investigation, provide justification for selecting "no", citing any regulatory guidance as applicable:

please complete this question

Is the device approved for marketing in the United States?

How is the device approved in the United States?

REQUIRED! Submit FDA Documentation in the Attachments Section

Select one of the following:

Is the device authorized for use under an FDA Emergency Use Authorization (EUA)?

Is the device being used in this study according to its approved indication?

Is the Device Exempt from the Investigational Device Regulations (21 CFR 812)?

Select the device exemption that meets one of the following categories:

Clarify how the device meets the category selected:

Is this device a Significant Risk (SR) device?

Has the investigator or sponsor of this research obtained an Investigational Device Exemption (IDE) from the FDA for the use of this device for this research?

REQUIRED! Submit the IDE Authorization Letter in the Attachments Section

IDE Number

Holder of the IDE (**check all that apply**):

Specify Lead Researcher:

Specify 'Other' IDE Holder:

Does the IDE allow billing of subjects?

Does the IDE cover a combination use (e.g., combination of an investigational drug and device)?

Specify the combination use:

Specify why an IDE has not been obtained yet:

Specify 'Other' reason:

Based on the criteria for a significant risk device listed in the link below, explain why the device as it is used in this study, qualifies as Non-Significant Risk (NSR) device:

Has the FDA or another IRB determined the device to be non-significant risk as it is used in this study?

Indicate who will be responsible for the management of the device during the study:

Explain the plan to ensure that the investigational device is used only in accordance with the UCI IRB approved protocol:

Indicate who will have access to the device and how access will be controlled to secure the device (or device stock):

Specify how records for control of the device (or device stock) will be recorded:

REQUIRED! Submit the Sponsor Device Log in the Attachment Section

Specify why no log will be used:

Indicate whether the investigational device is manufactured in a UCI facility:

Identify the lab and location:

You have completed the form for this medical device. Click the 'Done' button. If you need to add more devices, click on the + Add Line button above the table to enter additional devices.

Name of Device or Product

Magstim 200/220 Transcranial Magnetic Stimulator

Device Manufacturer

Magstim

Description of the device:

This is a TMS device that delivers magnetic impulse to the brain to trigger a neural response.

Specify the proposed use of the device for this study:

The purpose of this device is to identify if the subjects in the study have a connection between the brain motor cortex and the tibialis anterior muscle.

Does this device have an Instructions for Use/User Manual/Product Brochure?

Yes

REQUIRED! Submit the Instructions for Use, User Manual or Product Brochure in the Attachments Section

Include information to describe how it works and the foreseeable risks associated with its use:

Is the device a medical device?

Yes, this device is a medical device

If “no”, for minimal risk studies and the device is intended to be used in a clinical setting, provide justification for selecting “no”, citing any regulatory guidance as applicable:

Are you testing the safety and/or efficacy of this device?

No, the safety and/or efficacy of this medical device is not being assessed

If “no”, for minimal risk research and if the device is the object of the investigation, provide justification for selecting “no”, citing any regulatory guidance as applicable:

please complete this question

Is the device approved for marketing in the United States?

How is the device approved in the United States?

REQUIRED! Submit FDA Documentation in the Attachments Section

Select one of the following:

Is the device authorized for use under an FDA Emergency Use Authorization (EUA)?

Is the device being used in this study according to its approved indication?

Is the Device Exempt from the Investigational Device Regulations (21 CFR 812)?

Select the device exemption that meets one of the following categories:

Clarify how the device meets the category selected:

Is this device a Significant Risk (SR) device?

Has the investigator or sponsor of this research obtained an Investigational Device Exemption (IDE) from the FDA for the use of this device for this research?

REQUIRED! Submit the IDE Authorization Letter in the Attachments Section

IDE Number

Holder of the IDE (**check all that apply**):

Specify Lead Researcher:

Specify 'Other' IDE Holder:

Does the IDE allow billing of subjects?

Does the IDE cover a combination use (e.g., combination of an investigational drug and device)?

Specify the combination use:

Specify why an IDE has not been obtained yet:

Specify 'Other' reason:

Based on the criteria for a significant risk device listed in the link below, explain why the device as it is used in this study, qualifies as Non-Significant Risk (NSR) device:

Has the FDA or another IRB determined the device to be non-significant risk as it is used in this study?

Indicate who will be responsible for the management of the device during the study:

Explain the plan to ensure that the investigational device is used only in accordance with the UCI IRB approved protocol:

Indicate who will have access to the device and how access will be controlled to secure the device (or device stock):

Specify how records for control of the device (or device stock) will be recorded:

REQUIRED! Submit the Sponsor Device Log in the Attachment Section

Specify why no log will be used:

Indicate whether the investigational device is manufactured in a UCI facility:

Identify the lab and location:

You have completed the form for this medical device. Click the 'Done' button. If you need to add more devices, click on the + Add Line button above the table to enter additional devices.

Name of Device or Product

A time-resolved near infrared spectroscopy (TR-NIRS) device

Device Manufacturer

TRS-21; Hamamatsu Photonics

Description of the device:

A time-resolved near infrared spectroscopy (TR-NIRS) device (TRS-21; Hamamatsu Photonics) will be used to acquire metabolic measurements (e.g., tissue hemoglobin concentration and oxygenation) at the TA muscle. This device is noninvasive, consisting of two source fibers connected to light sources in the visible to near infrared wavelength range, and two detector fibers to collect backscattered photons and direct them to a photodetector. The output is connected to a computer to provide data acquisition and handling. The source and detector fibers are mounted within tethered pads that adhere to the surface of the skin.

Specify the proposed use of the device for this study:

TR-NIRS parameters will be measured at the TA muscle of stroke patients while they attempt dorsiflexion while seated with the tibia perpendicular to the ground. Measurements pertaining to oxygen metabolism at the TA muscle will be acquired by placing the source and detector fibers on the skin surface positioned over the muscle (using the adhesive pads). This setup allows for the collection of metabolic data in real time while either the BCI-FES or BCI-robotic orthosis systems are being used.

Does this device have an Instructions for Use/User Manual/Product Brochure?

Yes

REQUIRED! Submit the Instructions for Use, User Manual or Product Brochure in the Attachments Section

Include information to describe how it works and the foreseeable risks associated with its use:

Is the device a medical device?

No, this is not a medical device

If “no”, for minimal risk studies and the device is intended to be used in a clinical setting, provide justification for selecting “no”, citing any regulatory guidance as applicable:

The device is not intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals. The device is approved for clinical research and it has been used in clinical research settings as an investigational device. So we will not be testing it's saftey as it has already been proven to be safe. We are not testing the efficacy of the device. It is a monitoring device that does not provide any treatment or intervention. This device will report changes in subject's: oxy-hemoglobin, deoxy-hemoglobin, total hemoglobin and oxygen saturation.

Are you testing the safety and/or efficacy of this device?

If “no”, for minimal risk research and if the device is the object of the investigation, provide justification for selecting “no”, citing any regulatory guidance as applicable:

Is the device approved for marketing in the United States?

How is the device approved in the United States?

REQUIRED! Submit FDA Documentation in the Attachments Section

Select one of the following:

Is the device authorized for use under an FDA Emergency Use Authorization (EUA)?

Is the device being used in this study according to its approved indication?

Is the Device Exempt from the Investigational Device Regulations (21 CFR 812)?

Select the device exemption that meets one of the following categories:

Clarify how the device meets the category selected:

Is this device a Significant Risk (SR) device?

Has the investigator or sponsor of this research obtained an Investigational Device Exemption (IDE) from the FDA for the use of this device for this research?

REQUIRED! Submit the IDE Authorization Letter in the Attachments Section

IDE Number

Holder of the IDE (**check all that apply**):

Specify Lead Researcher:

Specify 'Other' IDE Holder:

Does the IDE allow billing of subjects?

Does the IDE cover a combination use (e.g., combination of an investigational drug and device)?

Specify the combination use:

Specify why an IDE has not been obtained yet:

Specify 'Other' reason:

Based on the criteria for a significant risk device listed in the link below, explain why the device as it is used in this study, qualifies as Non-Significant Risk (NSR) device:

Has the FDA or another IRB determined the device to be non-significant risk as it is used in this study?

Indicate who will be responsible for the management of the device during the study:

Explain the plan to ensure that the investigational device is used only in accordance with the UCI IRB approved protocol:

Indicate who will have access to the device and how access will be controlled to secure the device (or device stock):

Specify how records for control of the device (or device stock) will be recorded:

REQUIRED! Submit the Sponsor Device Log in the Attachment Section

Specify why no log will be used:

Indicate whether the investigational device is manufactured in a UCI facility:

Identify the lab and location:

You have completed the form for this medical device. Click the 'Done' button. If you need to add more devices, click on the + Add Line button above the table to enter additional devices.

Risk Assessment

Risks and Discomforts

1. Describe and assess any reasonably foreseeable risks and discomforts associated with each procedure for each subject population — physical, psychological, social, legal or other:

2. If this study will involve the collection of identifiable private information, even temporarily, for which the disclosure of the data outside of the research could reasonably place the subjects at risk, include the risk of a potential breach of confidentiality:

As listed in the 3 Consents for this study (Screening Consent, Full Study Group 1 and 2 Consent, Full Study Group 3 and 4 Consent).

Risk in Screening
No long-term side effects are anticipated as part of the screening examinations. There is a low risk of fatigue associated with undergoing the examination. The test of electrical stimulation on your leg muscles may lead to some temporary discomfort, although this risk is very low. There is also a low risk of falling when asked to walk without leg prostheses during the physical exam.

Risk in Aim 1 and 2 (Groups 1 and 2)

Risks and side effects related to the BCI-FES therapy include those which are:
- Discomfort with wearing EEG electrodes (unlikely)
- Increased falls (highly unlikely)
- Fatigue (unlikely)
- Skin breakdown due to electrical stimulation (highly unlikely)

Risks and side effects related to physical therapy include:
- Falls during therapy (highly unlikely)
- Physical injury during therapy (highly unlikely)
- Fatigue (unlikely)

Risks and side effects related to detailed physical examinations:
- Discomfort due to performing tasks (unlikely)
- Falls due to walking during exams (highly unlikely)

Risk in Aim 3 (Group 3 and 4)
Risks and side effects related to the BCI-FES operation include those which are:
- Discomfort with wearing EEG electrodes (unlikely)
- Increased falls (highly unlikely)
- Fatigue (unlikely)
- Skin breakdown due to electrical stimulation (highly unlikely)

Risks and side effects related to the BCI-Robot operation include those which are:
- Discomfort with wearing EEG electrodes (unlikely)
- Increased falls (highly unlikely)
- Fatigue (unlikely)

Risks and side effects related to detailed physical examinations:

- Discomfort due to performing tasks (unlikely)
- Falls due to walking during exams (highly unlikely)
- Skin irritation due to TR-INR device (highly unlikely)

Discuss what steps have been taken and/or will be taken to prevent and minimize any risks/potential discomforts to subjects:

Subjects who are enrolled in the study will have been screened to ensure that they meet the study criteria above. Meeting these criteria will minimize the risks associated with participation. Additional measures will be taken to minimize the risks described above. More specifically, the physical risk of fall and injury resulting from the fall will be minimized given that the gait assessments and physiotherapies are performed with standard techniques and by qualified practitioners. Furthermore, any discomfort resulting from stimulation techniques (FES, TMS) will addressed by reducing the stimulation intensity until discomfort is eliminated. Dr. Do (lead researcher), and Lucy Dodakian (study coordinator), will be responsible for safety oversight of the study.

Certificate of Confidentiality

Is the research partially or wholly funded by NIH (including NIH Institutes and Centers), or does the research involve identifiable sensitive information that require CoC protections?

Yes

Indicate whether the research is protected by a NIH Certificate of Confidentiality (CoC):

This research is partially or wholly funded by NIH, including NIH Institutes and Centers. A CoC is automatically issued

Indicate in what situations identifiable private information protected by a CoC will be disclosed (check all that apply):

As required by Federal, State, or local laws, excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others

Potential Benefits

Is there the prospect of a direct benefit anticipated for subjects?

Yes

Describe the potential benefits subjects may expect to receive from participation in this study:

Undertaking BCI-FES therapy may provide improvement in gait velocity to the subjects. Undertaking the conventional physiotherapy components of the study may also provide improvement in gait function. Given the low risks associated with the study and the potential benefits of improvement in gait function, the risk-benefit ratio for participation is considered to be reasonable.

Specify the expected potential societal/scientific benefit(s) of this study:

If the BCI-FES therapy technique is found to be potentially efficacious, this may in the future benefit other stroke patients and society by providing a novel therapy to help reduce stroke-related disabilities and the associated public health burden.

Alternatives to Participation

Describe the alternatives to participation in the study available to prospective subjects. Include routine (standard of care) options as well as other experimental options, as applicable (**check all that apply**):

Routine standard of care available

Specify the routine standard of care:

physical therapy or at home exercise

Participant Compensation

Will subjects be compensated?

Yes

Specify whether compensation is applicable and, if so, the method, amount and schedule of compensation (Check all that apply):

Cash

Check

Gift Card

Cash Compensation

Specify cash amount:

Total compensation for participation in the entire study is $100.

Cash schedule:

Other

Specify 'Other' cash schedule:

Compensation is provided at the end of study participation. If subjects decide to withdraw from the study or are withdrawn by the research team, they will receive compensation for the visits that they have completed

Will the cash compensation method include all subjects?

Yes

Specify check amount:

Compensation will be provided to subjects in the form of a check issued to the subjects through the UCI Accounting Office. The subject's name, address, and social security number, will be released to the UCI Accounting Office for the purpose of payment and for tax reporting to the Internal Revenue Service (IRS). Total compensation for participation in the entire study is $100.

Check schedule:

Other

Specify 'Other' check schedule:
Compensation is provided at the end of study participation. If subjects decide to withdraw from the study or are withdrawn by the research team, they will receive compensation for the visits that they have completed

Will the check compensation method include all subjects?
Yes

Specify gift card type and amount:
Total compensation for participation in the entire study is $100.

Gift Card schedule:
Other

Specify 'Other' gift card schedule:
Compensation is provided at the end of study participation. If subjects decide to withdraw from the study or are withdrawn by the research team, they will receive compensation for the visits that they have completed

Will the gift card compensation method include all subjects?
Yes

Will subjects be reimbursed for out-of-pocket expenses?
No

Participant Costs

Will subjects or their insurers be charged for study procedures?
No

Confidentiality of Research Data

Information and/or Biospecimens Storage

Indicate how information and/or biospecimens (including signed consent forms) will be stored (check all that apply):

Information will be maintained electronically. Information will be password protected and maintained in an encrypted format

Encrypted Format

Specify where the information will be maintained electronically:

Secure data server will be kept in Engineering Gateway 3121.

Will subject/patient identifiers be collected or retained?

Yes

Subject/Patient Identifiers

Will any subject/patient identifiers be collected or retained for data analysis, recruitment, consenting and/or compensation (check all that apply)?

All elements of dates (except year) for dates that are directly related to an individual: birth date, admission date, discharge date, death date, and all ages over 89
Email addresses
Full-face photographs and any comparable images
Medical record numbers
Names
Telephone numbers

Will a code be used to link subject/patient identifiers with the information and/or biospecimens?

A code will be used. Subject/Patient identifiers will be kept separately from the information and/or biospecimens. The code key will be destroyed at the earliest opportunity, consistent with the conduct of this research

Will research data/biospecimens be transported or maintained on portable devices (e.g., laptop, smartphone, external hard drive, etc.)?

No

Specify who will have access to subject/patient identifiable information/biospecimens as part of this protocol (**check all that apply**):

Authorized UCI personnel (such as the research team) and appropriate institutional officials: such as the Office of Human Research Protections (OHRP) Regulatory entities such as the Food and Drug Administration (FDA), the National Institutes of Health (NIH)

Specify whether subject/patient identifiers be disclosed in presentations and/or publications:

Subject/Patient identifiers will not be disclosed

Specify how long all subject/patient identifiers will be retained. This includes identifiers stored in paper format, stored electronically as well as video recordings, audio recordings, photographs, etc.:

Other

Specify 'Other' time frame and provide rationale:

The researchers intend to keep the research data indefinitely. The researchers may continue to use and share the information and information obtained from analyses of the information indefinitely

Will any identifiable photos or audio/video recordings be collected or used?

Yes

Collection of Photographs, or Audio/Video Retention & Recording

Will identifiable audio recordings be collected?

Yes

How will the audio recordings be transcribed?

Identifiable audio recordings transcribed by the study team

Specify timeframe for the audio transcription:

Identifiable audio recordings will be transcribed by the study team within 1 week.

Will the identifiable audio recordings be de-identified?

Yes

Specify timeframe for the audio recordings de-identification and how will the recordings be de-identified:
De-identified version will be maintained indefinitely in case of need for future research/publication

Will identifiable video recordings be collected?
Yes

How will the video recordings be transcribed?
Identifiable video recordings transcribed by the study team

Specify timeframe for the video transcription:
within 7-14 days

Will the identifiable video recordings be de-identified?
Yes

Specify timeframe for the video recordings de-identification and how will the recordings be de-identified:
De-identified version will be maintained indefinitely in case of need for future research/publication

Will identifiable photographs be collected?
Yes

Will the identifiable photographs be de-identified?
Yes

Specify timeframe for the photographs de-identification and how will the photographs be de-identified:
De-identified version will be maintained indefinitely in case of need for future research/publication

Research Information and/or Biospecimens Retention

Indicate how long research information/biospecimens will be retained:
In addition, if the research involves the investigation of FDA regulated products, information/biospecimens will be retained for two years after an approved marketing application. If approval is not received, the information/biospecimens will be kept for 2 years after the investigation is discontinued and the FDA is notified per FDA sponsor requirements

Will research information and/or biospecimens be shared?

No

Attachments

If required documentation is not provided, the submission is incomplete and your Application will be returned to you. Be sure to upload each document as required. If changes are needed, go back to the sub-section to revise your selections.

Maximum file size is 30MB

All UCI templates are available on the Human Research Protections Applications & Forms page or Human Stem Cell Research Applications & Forms page.

To access approval documents where UCI will rely on another IRB, including commercial IRBs, visit their respective online portals. Frequently used commercial IRB portals include:

- WIRB Copernicus Group's WCG IRB Connexus
- Advarra's CIRBI
- SMART Online Reliance System (ORS)

Attachment

2019-4936 email to confirm no COIOC review is required_normal_352530.pdf

Attachment Type

File Comments

File Name

Status (IRB/hSCRO Use Only)

Attachment

2019-4936 Neuro-QOL Item Bank v1.0 - Lower Extremity Function (Mobility) v02-27-18_normal_372029.pdf

Attachment Type

Data Collection Tool/Instrument

File Comments

File Name

Status (IRB/hSCRO Use Only)

Attachment

20194936 HIPAA Authorization_11-09-22.docx

Attachment Type

HIPAA Research Authorization Form

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

2019-4936 Facebook Ad 12-02-20_normal_400073.pdf

Attachment Type

Recruitment Material

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

2019-4936 Facebook Ad 12-02-20_approved_400073.pdf

Attachment Type

Recruitment Material

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

20194936 Screening Consent 10-11-24.docx

Attachment Type

Consent Form

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Add

Attachment

20194936 Screening Consent and HIPAA 10-11-24.pdf

Attachment Type

Consent Form

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

20194936 Groups 1 & 2 Consent 10-11-24.docx

Attachment Type

Consent Form

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Add

Attachment

20194936 Groups 1 & 2 Consent and HIPAA 10-11-24.pdf

Attachment Type

Consent Form

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

2019-4936 UCIMC Clinic Trials Web Page Ad 12-02-20_normal_400076.docx

Attachment Type

Recruitment Material

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

2019-4936 UCIMC Clinic Trials Web Page Ad 12-02-20_approved_400076.pdf

Attachment Type

Recruitment Material

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

2019-4936 Recruitment Flyer 12-02-20_normal_400078.doc

Attachment Type

Recruitment Material

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

2019-4936 Recruitment Flyer 12-02-20_approved_400078.pdf

Attachment Type

Recruitment Material

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

2019-4936 Recruitment Letter to Referring HealthCare Professional 12-02-20 (NO STAMPING)_normal_400080.docx

Attachment Type

Recruitment Material

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

20194936 Procedure Table 06-22-2023.docx

Attachment Type

Other

File Comments

File Name

Status (IRB/hSCRO Use Only)

Attachment

TMS_Magstim 200_262 Operating Manual 3001-23-04.doc.pdf

Attachment Type

Medical Device Instructions (User Manual/Product Brochure)

File Comments

File Name

Status (IRB/hSCRO Use Only)

Add

Attachment

DSMB Charter_20231017.pdf

Attachment Type

Data Safety Monitoring Plan Documentation

File Comments

Revised

File Name

Status (IRB/hSCRO Use Only)

Attachment

AMPD SOP_V6.docx

Attachment Type

Medical Device Picture

File Comments

Ankle Measuring Proprioception Device (AMPD) Manual

File Name

Status (IRB/hSCRO Use Only)

Add

Attachment

BCI-FES Protocol.docx

Attachment Type

Medical Device Instructions (User Manual/Product Brochure)

File Comments

File Name

Status (IRB/hSCRO Use Only)

Add

Attachment

TR-NIRS device_Manual.pdf

Attachment Type

Medical Device Instructions (User Manual/Product Brochure)

File Comments

File Name

Status (IRB/hSCRO Use Only)

Add

Attachment

20194936 HIPAA Authorization_11-09-22.pdf

Attachment Type

HIPAA Research Authorization Form

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

20194936 Groups 3 & 4 Consent 10-11-24 .docx

Attachment Type

Consent Form

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Add

Attachment

20194936 Groups 3 & 4 Consent and HIPAA 10-11-24.pdf

Attachment Type

Consent Form

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

DSMB_interrim_report_BCI_20230917_dvn.pdf

Attachment Type

Data Safety Monitoring Plan Documentation

File Comments

File Name

Status (IRB/hSCRO Use Only)

Add

Attachment

DSMB_Approval_2023.pdf

Attachment Type

Data Safety Monitoring Plan Documentation

File Comments

File Name

Status (IRB/hSCRO Use Only)

Add

Attachment

20194936 Renewal Approval Letter 10-11-24.pdf

Attachment Type

UCI IRB Approval Letter

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Lead Researcher Certification

Investigator's Assurance

As Lead Researcher, I have ultimate responsibility for the performance of this study, the protection of the rights and welfare of the human subjects, and strict adherence by all co-investigators and research personnel to all Institutional Review Board (IRB) requirements, federal regulations, and state statutes for research involving human subjects.

I hereby assure the following:

1. The information provided in this application is accurate to the best of my knowledge.
2. The information provided in this application has been discussed and shared with my Department Chair. Any requests for changes based on this discussion are included in this application upon submission or will be initiated by the research team either during the IRB review process or via an amendment.
3. All named individuals on this project have read and understand the procedures outlined in the protocol and their role on the study.
4. All named individuals on this project have completed the required Educational research tutorials and have been made aware of the "Common Rule" (45 CFR Part 46), applicable Food and Drug Administration (FDA) regulations (21 CFR Parts 50, 56, 312 and 812), have read the Belmont Report, and UCI's Federalwide Assurance (FWA) that are available on the Human Research Protections Program (HRP) website.
5. All experiments and procedures involving human subjects will be performed under my supervision or that of another qualified professional listed on this protocol.
6. I understand that, if the study described in this IRB application is supported by a federal award or used as a basis for a proposal for funding, it is my responsibility to ensure that the description of human subjects activities in the proposal/award is identical in principle to that contained in this application. I will submit modifications and/or changes to the IRB as necessary to assure the proposal/award and application are identical in principle.

I and all co-investigators and research personnel agree to comply with all applicable requirements for the protection of human subjects in research including, but not limited to, the following:

1. Obtaining the legally effective informed consent of all human subjects or their legally authorized representatives (unless waived) and using only the currently approved, stamped consent form (if applicable).
2. Per federal regulations, once a human research study has received IRB approval, any subsequent changes to the study must be reviewed and approved by the IRB prior to implementation except when necessary to avoid an immediate, apparent hazard to a subject. See Reporting of Unanticipated Problems.
3. Reporting any unanticipated problems involving risk to subjects or others, including protocol violations per UCI IRB policy. In addition, HIPAA privacy violations must be PROMPTLY disclosed to the UCI Privacy Officer. There are time requirements for reporting these breaches of confidentiality, which, if not met, may result in monetary damages to the researcher and the institution.
4. Responding appropriately to subjects' complaints or requests for information about the study; and reporting to the IRB any subject complaints that are not resolvable by the study

team.

5. Promptly providing the IRB with any information requested relative to the project.
6. Assuring the appropriate administration and control of investigational test articles (i.e., investigational drugs, biologics or devices) by a qualified investigator or other appropriate individual or entity (e.g., UCI Health pharmacy), and assuring use and maintenance of an Investigational Drug/Biologic Accountability Log or Device Accountability Log.
7. Registering applicable clinical trials with clinicaltrials.gov. For more information about this topic, visit the ClinicalTrials.gov web page or the HRP webpage. The consequences of not meeting the registration and reporting requirements include monetary damages to the researcher and the institution.
8. Obtaining continuing review prior to study expiration (I understand if I fail to apply for continuing review, approval for the study will automatically expire, and all human research activities must cease until IRB approval is obtained).
9. Promptly and completely complying with an IRB decision to suspend or terminate its approval for some or all research activities.
10. Submitting to a routine review of human subject research records. The Compliance & Privacy Office at UCI Health performs ongoing routine reviews of open biomedical research protocols, in an effort to ensure in part that human subject research activities are conducted in accordance with regulations, laws and institutional policies regarding the protection of human subjects. In addition, the HRP unit of the Office of Research has developed the Education Quality and Improvement Program (EQUIP). Through EQUIP, HRP staff conduct periodic quality improvement monitoring and educational outreach.
11. For clinical trials initially approved by the IRB on or after January 21, 2019, posting one (1) IRB-approved clinical trial consent form at a publicly available federal website. The consent form must be posted after recruitment closes, and no later than 60 days after the last study visit. For additional guidance, refer to the OHRP FAQs on Informed Consent.
12. Filing a final report with UCI HRP at the conclusion of this project.

As the Lead Researcher, I assure all of the above

Financial Disclosure

Investigators' Disclosure of Financial Interest

In order to inform research subjects of circumstances that may affect their decision to participate in this study, all researchers are required to disclose their financial interests with outside institutions.

The Lead Researcher of the protocol must ask the following question of all study team members:

"Do you, your spouse/registered domestic partner, and dependent children together have any disclosable financial interests (i) that would reasonably appear to be affected by the research; or (ii) in entities whose financial interests would reasonably appear to be affected by the research?"

A member of the study team who answers in the affirmative will be contacted by the Conflict of Interest Oversight Committee (COIOC) to obtain additional information regarding their specific financial interest(s).

IMPORTANT! If there has been a change in the financial disclosures of the LR or the study team, please also request a 'Change in Financial Interests'.

As Lead Researcher, I certify that the disclosures for all study team members are accurate

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End of form. Please review responses for accuracy and completeness.

Please ignore the Admin Details Section below. This section is for IRB/hSCRO use only.

Administrative Details Form

Project Status

Committee:
IRB B

Project Status:
Approved

Date of Project Determination:
October 11, 2024

Amendment Status:
Approved

Date of Amendment Determination:
June 22, 2023

Date of ERA Transcription:
November 11, 2021

Pre-2018 Common Rule:
No

Date of Transition to 2018 Common Rule:
No date entered