A. COVER PAGE

Project Title: Agonist-Antagonist Myoneural Interface for Functional Limb Restoration after Transtibial Amputation	
Grant Number: 5R01HD097135-05	**Project/Grant Period:** 03/14/2019 - 02/29/2024
Reporting Period: 03/01/2023 - 02/29/2024	**Requested Budget Period:** 03/01/2023 - 02/29/2024
Report Term Frequency: Final	**Date Submitted:** 07/30/2024
Program Director/Principal Investigator Information: HUGH M HERR , MS PHD BA **Phone Number:** (617) 253-6780 **Email:** hherr@media.mit.edu	**Recipient Organization:** MASSACHUSETTS INSTITUTE OF TECHNOLOGY MASSACHUSETTS INSTITUTE OF TECHNOLOGY 255 Main Street NE18-901 CAMBRIDGE, MA 021421029 **DUNS:** 001425594 **UEI:** E2NYLCDML6V1 **EIN:** 1042103594A1 **RECIPIENT ID:**
Change of Contact PD/PI: NA	
Administrative Official: NANCY A SAHAGIAN 77 Massachusetts Avenue, NE18-901 Cambridge, MA 021394307 **Phone number:** 617-715-4295 **Email:** nsahag@MIT.EDU	**Signing Official:** BERNADETTE VALLELY 77 Massachusetts Ave Office of Sponsored Programs NE18-901 Cambridge, MA 02139 **Phone number:** 617-324-7211 **Email:** bvallely@mit.edu
Human Subjects: Yes **HS Exempt:** NA **Exemption Number:** **Phase III Clinical Trial:** NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

	Massachusetts Institute of Technology Committee on the Use of Humans as Experimental Subjects	**Protocol #** (assigned by COUHES)	1812634918

APPLICATION FOR USE OF HUMANS AS EXPERIMENTAL SUBJECTS
(STANDARD FORM)

*Please answer every question. Positive answers should include details. N/A must be marked where the question does not pertain to your application. Any incomplete application will be rejected and returned for completion. This application **must** include the secondary personnel list form otherwise this application will be returned to you.*

I. BASIC INFORMATION

1. Title of Study

NIH Study of Neural Control of a Bionic 2-DoF Ankle-Foot Prosthesis

2. Principal Investigator

Name: [redacted]	Building and Room #: E14-374
Title: Professor	Email:
Department: Media Arts & Sciences	Phone: [redacted]

3. Funding. *If the research is funded by an outside sponsor, please enclose one copy of the research proposal with your application. A draft of the research proposal is acceptable.* ***Do not leave this section blank. Check all that apply. If your project is not funded, check No Funding.***

A. Sponsored Project Funding:

☐ Current Proposal Grant/Proposal #_____
Sponsor _____
Title _____

☒ Current Award Grant/Account # 1R01-HD097135 / 6940415
Sponsor National Institutes of Health – National Institute for Child Health & Development
Title "Agonist-Antagonist Myoneural Interfaces for Functional Limb Restoration after Transtibial Amputation"

B. Institutional Funding:

☒ Gift ☐ Departmental Resources
☐ Other (explain) _____

C. No Funding

☐ This protocol will not be funded

4. STATEMENT OF FINANCIAL INTEREST

Does the investigator, study personnel involved in the study or their family have a financial interest in a company or other organization participating in or providing drugs, devices, biological agents, investigational medical devices, or any other tangible material or financial sponsorship for the research?

☐ Yes ☒ No

Does this study contemplate receiving/using any materials/data (data sets, confidential information) or making any purchases from or subawards to a company or other organizations in which you or a family member hold a Financial Interest?

☐ Yes ☒ No

If yes was checked for any of the questions above, then attach a **Supplement for Disclosure of Financial Interest** for each individual with an interest. *This supplement, together with detailed guidance on this subject and definitions of the highlighted terms, is available in the COUHES site under Policies & Procedures in the Financial Conflicts of Interest section.*

5. Anticipated Dates of Research

Start Date: 03/01/2019	Completion Date: 02/28/2025

6. Collaborating Institutions. *If you are collaborating with another institution(s) then you must obtain approval from that institution's institutional review board, and forward copies of the approval to COUHES.*

Not Applicable

7. Location of Research. *If at MIT please indicate where on campus. If you plan to use the facilities of the Clinical Research Center you will need to obtain separate approval from the MIT Catalyst Clinical Research Center.*

MIT Media Laboratory E14-274, E15-463

II. STUDY INFORMATION

1. Purpose of Study. *Please provide a concise statement of the background, nature and reasons for the proposed study. Use non-technical language that can be understood by non-scientist members of COUHES.*

Loss of limb profoundly impacts the physical and emotional health of nearly two million Americans at an annual cost exceeding 250 million dollars. The vast majority of the people living with limb loss have affected lower limbs. Outcomes of limb amputations are limited by prosthesis interfacing technologies. Toward reinstating aspects of motor and sensory functions in persons with transtibial (TT) amputation, the Agonist-antagonist Myoneural Interface (AMI) was developed and first studied at the TT (*i.e.,* below knee) amputation level through collaboration between MIT and the Brigham & Women's Hospital (BWH). An AMI is comprised of two muscles – an agonist and an antagonist – that are surgically connected in series within the residual limb during an experimental BKA such that contraction of one muscle stretches the other. Two AMI constructs are created in the residual limb: one AMI directly links the *lateral gastrocnemius* (LG) and the *tibialis anterior* (TA) muscles toward improving motor control and sensation of a virtual or prosthetic ankle joint, and the other AMI

directly links the *peroneus longus* (PL) and the *tibialis posterior* (TP) muscles toward improving motor control and sensation of a virtual or prosthetic subtalar joint. This surgical architecture is designed to preserve musculotendinous sensors and anatomical muscle relationships that evolved to provide bi-directional communication of neural signals post-amputation. The TT AMI amputation is also anticipated to yield more isolated electromyography (EMG) signals resulting from residual limb muscle activations towards improved myoelectric control of a prosthetic device, and a myoneural interface for investigating proprioceptive sensations (*i.e.,* perceptions of the position, movement, and torque) of the phantom limb.

At the same time, next-generation wearable prostheses mimicking the physiological functions of the biological ankle-foot complex are under development in the MIT Biomechatronics group. One such system comprises flexible, socket-compatible EMG sensors, an embedded EMG data acquisition system, a mechatronic two degree-of-freedom (2-DoF) ankle-subtalar prosthesis with two on-board, high-torque motors to actuate ankle and subtalar joints, capability to measure joint state (i.e., position and speed) and sense joint torque, and an integrative electronics control platform. Beyond the intent to preserve range of motion after TT amputation in both the coronal and sagittal planes to allow more sophisticated balance control, clinical studies of TT amputation subjects that involve the 2-DoF prosthesis as data collection platform will yield novel EMG-modulated prosthetic control algorithms. The First human subject with a TT AMI amputation demonstrated a capacity for independent contraction of each AMI muscle, graded proprioceptive responses to controlled muscle activations, and a potential for closed-loop motor control of prosthesis in an experimental setting of force feedback [Clites, T.R. *et al., Science Transl. Med.* 2018, and Clites, TR *et al., PRS- Global Open* , 2018].

This study protocol is linked to the clinicaltrials.gov registration NCT03913273 and NIH-NICHD-NCMRR award R01-HD097135. The study has two arms and a prospective, non-randomized, non-blinded design. There is an AMI interventional arm with amputee subjects drawn from the pool of patients who previously underwent a TT amputation with construction of AMIs in their residual limb. There is also a Non-AMI active comparator arm with amputee subjects who previously underwent TT amputations without AMI constructs incorporated. Each Non-AMI subject is prospectively matched to an AMI subject to the degree possible based on age at the time of testing, elapsed time since amputation, and body habitus, although there are no formal exclusion criteria in this regard. Best efforts are made to include a diverse subject population. The clinical trial rigorously evaluates the capabilities of all amputee subjects in the study population regardless of the type of amputation performed through computational analyses and experimental testing of a next-generation wearable prosthesis platform. If motor control for tasks relevant to daily life and sensory feedback can be successfully provided then the TT AMI procedure and/or the 2-DoF prosthesis platform have the potential to improve overall health. Additionally, we expect to collect an invaluable set of data that may inform system component designs as well as neuromuscular control paradigms for next-generation lower extremity prostheses.

2. Study Protocol. *For* **biomedical, engineering and related research,** *please provide an outline of the actual experiments to be performed. Where applicable, provide a detailed description of the experimental devices or procedures to be used, detailed information on the exact dosages of drugs or chemicals to be used, total quantity of blood samples to be used, and descriptions of special diets. For applications in the* **social sciences, management and other non-biomedical disciplines** *please provide a detailed description of your proposed study. Where applicable, include copies of any questionnaires or standardized tests you plan to incorporate into your study. If your study involves interviews please submit an outline indicating the types of questions you will include.*
You should provide sufficient information for effective review by non-scientist members of COUHES. Define all abbreviations and use simple words. Unless justification is provided for additional length, this part of the application must not exceed 5 pages. Attaching sections of a grant application is not an acceptable substitute for a description of your study as requested here.

Overview

This study investigates the AMI TT amputation procedure and a prototype 2-DoF prosthesis with the intentions of evaluating motor control and proprioception in the residual limb in all amputee subjects as well as comparing AMI and Non-AMI subject outcomes. The study has three Specific Aims:
Aim 1. Investigate if AMIs can improve voluntary free-space prosthetic control;
Aim 2. Determine if AMIs improve voluntary and involuntary (reflexive) prosthetic terrain adaptations;
Aim 3. Explore if AMIs can serve as a bi-directional human-device interface.

Aim 1:

Capacity for voluntary free-space prosthetic control is evaluated for AMI and Non-AMI amputee subjects through a combination of time-synchronized temporospatial EMG and goniometry data as well as real-time ultrasonography scans, collected from subjects' residual limbs and biologically intact contralateral limbs. Bony anatomical landmarks and target muscles are identified by palpation and their superficial projections are marked using a skin marker and reflective marker balls. For residual limb mapping, and ultimately for motor control, surface EMG electrodes are placed on the affected and unaffected limbs to assess muscle activations, and goniometers are secured to the posterior aspect of the unaffected limb. For the free-space performance tasks, subjects are initially positioned in a supine recumbent position, and then seated in a chair with lower limb support as needed to allow full foot mobility. To assess motor control capacity, subjects are asked to perform ankle joint plantar flexion and dorsiflexion (PF and DF) and subtalar joint eversion and inversion (EV and IN) while mirroring the intended phantom limb motions with actual joint motions of the contralateral, unaffected lower limb.

Time-synchronized EMG and joint state data are simultaneously recorded during task performance to provide one-to-one temporospatial indicators of phantom limb efferent signaling and intended joint movement. As subjects demonstrate and mirror the range of motion (ROM) capacity for their phantom joint on their unaffected limb, time histories of PF and DF joint angles are measured using the 2-DoF goniometer attached across their biologically intact ankle joint. Residual limb muscle fascicle strains are recorded during PF, DF, EV, and IN motions for AMI and Non-AMI subjects using a high-definition ultrasound scanner at 60 fps. Positional discrimination tasks are used to assess subjects' capabilities for precise, graded movements of their phantom limb. Subjects perform graded

movements of their phantom limb over their full ROM in each direction and corresponding muscle activation levels are measured. Also, AMI construct muscle coupling is assessed for the AMI subjects by ultrasound tracking of opaque markers that were implanted within the constructs during the amputation surgery. Together, these data are used to create amputee-specific maps of the residual limbs and to develop neuromuscular models for more precise prosthetic joint motor control.

For initial mapping and model development studies the EMG data are collected at high density using up to 128 H124SG Ag/AgCl electrodes (Covidien) positioned in a grid-like fashion on the residual limb, and using electrodes positioned over the anatomical locations of the LG, TA, TP, and PL of the unaffected lower limb. The EMG data are acquired and processed using a physiological amplifier (Refa136, TMSi), the goniometry data are collected using the 2-DoF goniometer (Bio-Metrics), and ultrasound data are collected using a high-definition, 60 fps scanner (LS128, Telemed).

To assess free-space motor control in studies involving the 2-DoF prosthesis, AMI and Non-AMI subjects are seated in a chair and asked to follow position trajectories as presented on a graphical user interface (GUI). The 2-DoF prosthesis may either be located remotely or worn by the subject. In the latter case, thin flexible surface EMG electrodes are placed on the skin of the subject's residual limb at locations informed by data obtained in Aim 1. The EMG leads are threaded between the skin and the liner to exit the liner and socket, if worn, proximally. Subjects are asked to perform specific target- tracking tasks designed to explore the motion spaces of the ankle and subtalar joints by moving the prosthetic foot to point to a target position specified on the GUI, stiffening the limb to hold that position for a specified time interval, and repeating for additional targets. Tasks are performed with and without visual feedback. EMG data and joint position, speed, and impedance data are all collected in real-time. The EMG data are collected from eight to sixteen custom-fabricated flexible EMG sensors that are fixed to the subject's skin and under their own prosthetic liner, and in some tests the 2-DoF prosthesis is attached to their own prosthetic socket. The EMG data are acquired using a custom-fabricated, portable embedded system and goniometry data are collected using the 2-DoF Bio-Metrics system.

Aim 2:

Capacities for walking on level ground and performing real-life terrain adaptations are evaluated for AMI and Non-AMI amputee subjects through the use of techniques as already described for the Aim 1 (surface EMG acquired from within the subject's worn socket and goniometry) as well as a set of reflective markers to enable tracking of anatomical landmarks (e.g., hip, knee, ankle, foot). Subjects don the 2-DoF prosthesis and are given time to practice standing, balancing, and walking on a walkway equipped with handrails. The subjects then carry out and repeat specific ambulatory performance tasks. In one task, the subject performs a terrain obstacle maneuver involving everting the prosthetic subtalar joint such that the lateral edge of the prosthetic foot contacts the vertically offset block during the swing phase of the step while the medial edge of the prosthetic foot remains at the base height. In a second task, the subject ascends stairs in sequential steps. In a third task, the subject descends stairs in sequential steps.

To assess voluntary and involuntary (reflexive) motor control during the performance tasks, EMG data, kinematic, and kinetic data are collected in real-time. Kinetic data are collected from on-board prosthesis sensors. Also, the following force or motion sensors may be used to collect data: (i)

pressure-sensitive insoles inserted into one or both shoes worn by the subject along with associated electronics, (ii) force-measuring load-cell between the socket and prosthesis, and (iii) inertial measurement units (small motion sensors). Additionally, data are collected from force platforms embedded in the terrain equipment (a force platform is like a sophisticated bathroom scale that can sense the forces applied to the ground by the subject). Kinematic data are collected wirelessly using a 12-camera motion capture system (MX-T40S, Vicon Motion Systems). Photographs are taken to enable visualization of anatomical landmarks as subjects perform tasks in a motion-capture space. Biometric data, including subject weight, height, limb-segment lengths and circumference are also collected to help interpret the aforementioned kinematic and kinetic data.

Aim 3:

To explore whether AMIs can serve as a bi-directional human-device interface and provide data that can advance science and enable precise prosthetic motor control, functional electrical stimulation (FES) is tested as a force feedback modality in an experimental setting. Only the AMI subjects and not the Non-AMI subjects participate in Aim 3. The experimental set-up involves the same pedal-pushing task and FES paradigm implemented under COUHES protocol 1609692618 (Herr) with promising results and without any adverse effects.

The pedal-pushing task involves instructing the subject to voluntary contract their AMI agonist muscles (in this case the LG, an ankle joint plantar flexor) and, based on the resulting prosthetic joint torque, applying FES to the AMI antagonist muscle (in this case the TA, an ankle joint dorsiflexor). Fine-wire electrode FES is selected for this task because the electrical current amplitude necessary for surface FES to elicit a meaningful muscle contraction is sufficiently high that crosstalk would interfere with the EMG electrodes that are required to implement prosthetic joint control. We default to electrodes affixed to the subjects' skin as the primary mode of collecting EMG data. In the event that the surface EMG is not sufficiently robust to carry out the trials, we will move to fine-wire electrodes. Several factors will be used to evaluate surface EMG signal robustness, including the signal-to-noise ratio, the degree of inter-muscular crosstalk, signal quality degradation, and consistency of electrode placement. (Final implementation of AMIs for torque feedback will likely leverage implanted electrodes, which are being used in clinical trials but are not yet FDA-approved devices).

Experienced clinicians (Matthew Carty and other IRB-approved clinicians) are involved in this research study and will contribute their clinical experience through locating target muscles within the subjects' residual limbs, placing the surface and fine-wire electrodes for EMG and FES, and collecting clinical research data such as ultrasound images. Their involvements in this study are limited to their MIT roles as Visiting Scientists and other MIT Affiliations. They will NOT provide any medical advice or treatment within the scope of this study.

Two single-use electrodes are provided pre-assembled with one 27-gauge needle in a sterile medical kit (Motion Lab Systems part 000318-130-30). The kit comprises two electrodes threaded through the lumen of one needle with the electrodes' tips crimped and bent backward at needle tip. The fine-wire electrodes are extremely fine, with a diameter of only 0.051 mm, and are acutely placed in the lower limb by an experienced clinician (Dr. Matthew Carty or another IRB-approved clinician). The subject volitionally moves the phantom or biological foot through DF, PF, EV, and IN motions, while the

clinician palpates the limb to identify the corresponding muscle of interest. Fine-wire electrodes are then inserted into each target muscle. Placement is verified electromyographically and via direct muscle stimulation; poorly-placed electrodes are removed and replaced. The needle is removed immediately after insertion, thereby placing the electrode tip in the muscle for the test session and allowing easy removal of the electrode as needed. In the event of two sequential trial days, the fine-wire electrodes may remain in place overnight. If this is to happen, the clinician will apply local antibiotic to the area of each electrode insertion site and will bandage the limb. The subject will be instructed not remove the bandage, not to use the socket overnight, and not to bear weight on the residual limb while it is bandaged. The subject will also be instructed to avoid any circumstance in which the bandage would become wet (i.e. showering, swimming, etc.) and is provided with either crutches or a wheelchair to use for the overnight period. If a problem or concern should arise during the overnight period, the clinician will be available by telephone. In this scenario, the electrodes are removed at the end of the second day and are left in place for a maximum of two trial days, or one overnight period.

The FES protocol involves delivering a periodic stream of mono- or bi-phasic electrical pulses to the muscle, causing it to contract. The FES protocol uses frequency-, current-, and pulse-width controlled medical grade equipment (DS-5, Digitimer) that is fully equipped with hard-stop settings. All stimulation settings will be maintained within historically safe limits and will be tuned to prevent subject discomfort. Relevant literature indicates that, for the fine-wire electrodes, average current densities not exceeding 10 microamperes/mm^2 show no increased tissue trauma over that incurred by passive electrodes. Current densities will be kept well within this safe range. The safe range for transcutaneous stimulation (through the surface electrodes) is much larger: commercially available transcutaneous muscle stimulation systems deliver stimulation with parameters in the following ranges: 0-to-100 milliamperes, 1-to-100 Hz, and a pulse width of 30-to 300 microseconds. To find subject-specific comfort limits, we begin at low stimulation amplitude and pulse width, and slowly increase intensity until the subject reports reaching a limit of comfortable stimulation or until safe limits are reached, whichever happens first. The lower of this value and the historically safe limits described above will provide a hard-stop reference for stimulation settings.

In one task, subjects are instructed to move their phantom ankle joint through a series of joint positions and stiffnesses (e.g. “move to 80% plantar flexion and stiffen to 50%”) in the absence of FES while EMG and ultrasound data are collected. In a second task, EMG and ultrasound data are collected from both the LG and the TA as FES is applied at various intensities to the TA, and the subject is asked to report the perceived phantom joint position and torque. In a third task, subjects are instructed to plantar flex the prosthetic ankle, thereby applying torque to a sensorized foot pedal. The prosthesis is mounted to an assembly that holds it in contact with the foot pedal, remote from the subject. Subjects are blindfolded and isolated from auditory input as they are asked to produce torque at varying levels of percent effort (i.e., 25, 50, 75, 100%), both with and without FES feedback. During task performance, EMG, goniometry, and ultrasongraphy data are collected from subjects’ affected and unaffected limbs.

<u>Additional information</u>

Subjects in the AMI intervention group will participate in 5 or 6 experimental sessions during the study, with 4 of these sessions requiring approximately 4 hours and the other 1 or 2 sessions requiring

up to 8 hours; Subjects in the Non-AMI control group will participate in 4 of the aforementioned sessions requiring approximately 4 hours each. Within a given session, individual performance tasks typically last for less than 5 minutes. The subject will be given rest breaks between trials. In addition, subjects may ask to rest or stop at any time. There is no time limitation between sessions.

Subjects will use a prototype powered, 2-DoF ankle-foot prosthesis in place of their customary ankle-foot prosthesis for the trial. The prosthesis has the capability of providing active neural control of both ankle and subtalar joints, and its controller can be adjusted through a wireless link. Prosthesis control settings may be modified by the researchers between trials or during a trial as the subject is walking. Subjects are given as much time as necessary to practice using the prosthesis before the data collection begins.

3. Drugs and Devices. *If the study involves the administration of an investigational drug that is not approved by the Food and Drug Administration (FDA) for the use outlined in the protocol, then the principal investigator (or sponsor) must obtain an Investigational New Drug (IND) number from the FDA. If the study involves the use of an approved drug in an unapproved way the investigator (or sponsor) must submit an application for an IND number. Please attach a copy of the IND approval (new drug), or application (new use.).*

If the study involves the use of an investigational medical device and COUHES determines the device poses significant risk to human subjects, the investigator (or sponsor) must obtain an Investigational Device Exemption (IDE) number from the FDA.

Will drugs or biological agents requiring an IND be used? YES ☐ NO ☒
If yes, please provide details:

Will an investigational medical device be used? YES ☒ NO ☐
If yes, please provide details: The FDA considers an investigation of a Non-Significant Risk device to have an approved IDE when an IRB concurs with the Non-Significant Risk determination and approves the study. MIT COUHES considers the 2-DoF prosthesis to be used in the current application to be a Non-Significant risk device here, as well as in another of our protocols #1609692618 (Herr).

The battery-powered 2-DoF ankle-foot prosthesis comprises a pair of on-board motors that are used in parallel to actuate both the ankle and subtalar joints, and embedded sensors. The high-torque brushless motors reduce the required transmission ratio, resulting in a quiet, efficient, robust design. The 2-DoF ankle-foot prosthesis is attached to the subject's customary prosthetic socket.

4. Radiation *If the study uses radiation or radioactive materials it may also have to be approved by the Committee on Radiation Exposure to Human Subjects (COREHS). COUHES will determine if you need COREHS approval.*

Will radiation or radioactive materials be used? YES ☐ NO ☒
If yes, please provide details:
Will any type of lasers be used YES ☐ NO ☒
If yes, please provide details:

5. Diets

Will special diets be used? YES ☐ NO ☒
If yes, please provide details

III. PERSONNEL

Fill out the personnel list at the end of this form. *If the personnel list is not included, the application will be returned to you.*

IV. HUMAN SUBJECTS

1. Subjects (*that will be consented for this study*)

A. Maximum number of subjects: 32

Adults: 32 **Minors:** 0

B. Age(s): Minimum Age: 18 years
Maximum Age: 65 years

C. Inclusion/exclusion criteria

i. What are the criteria for inclusion or exclusion? This NIH study calls for eleven participants in each of two groups - intervention and control. The intervention group includes AMI subjects who have previously undergone a BKA during which two AMIs are surgically reconstructed within the residual limb at the time of an experimental "AMI amputation". Currently, AMI amputations are only being done under IRB approval at the Brigham and Women's Hospital (BWH) by Dr. Matthew Carty. Carty is an MIT Visiting Scientist on our team and a Staff Surgeon at BWH. The control group includes Non-AMI subjects who have previously undergone standard BKA surgery, and are prospectively matched to an AMI subject based on the time since amputation, body habitus, and age. Additional study inclusion criteria include: (i) generally good health without any significant respiratory or other health problems that significantly impair normal ambulatory function, (ii) demonstration of full healing at the amputation site, which is generally achieved approximately three months following amputation, (iii) proficient use of a standard lower extremity prosthesis, and (iv) capability to ambulate with variable cadence at a "K" level of at least K3 to K4). Tobacco users, pregnant women, and children are excluded.

ii. Are any inclusion or exclusion criteria based on age, gender, or race/ethnic origin?
If so, please explain and justify. Our subject criteria are non-exclusive in that we consider participants of any sex/gender, race, and/or ethnic orientation.

iii. Please explain the inclusion of any vulnerable population (e.g. children, cognitively impaired persons, non-English speakers, MIT students), and why that population is being studied.
Children are excluded from the AMI subject cohort in this study due to the fact that pediatric patients are not eligible to undergo the required precursor surgical procedure. The AMI surgery is an

experimental operation that currently is only being done with IRB approval at the BWH, and the BWH is an adult-only facility; pediatric patients are therefore not approved to undergo the AMI surgery. Due to the matching criteria that have been established for the identification of Non-AMI control subjects in this study, which include patient age, children are also excluded from the Non-AMI subject cohort.

Due to the matching criteria with AMI and non-AMI cohorts, children are also excluded from the intact subject cohort.

2. Subject recruitment *Identification and recruitment of subjects must be ethically and legally acceptable and free of coercion. Describe below what methods will be used to identify and recruit subjects. Attach any and all recruitment documents associated with the protocol (i.e. flyers, e-mails, advertisements, etc.)*

The subjects in the intervention group will be drawn from the pool of patients who have undergone an experimental "AMI Amputation" at the BWH, as described above, in the Inclusion Criteria section. The BWH IRB-approved protocol covering the AMI Amputation includes as an enrollment criterion the willingness to undergo testing at MIT under a separate protocol approved by MIT's IRB (COUHES) because some of the data needed to help validate the surgery is being collected at MIT. The subjects in the control group will be drawn from patients who have undergone a standard BKA procedure at either the BWH or another hospital. Recruitment will be done via flyers, word of mouth, referrals, and external inquiries that our research group receives from the general public. We shall directly contact individuals who have already worked on our studies, certified prosthetists, and rehabilitation centers. We will leverage the professional networks of the PI, Herr (an academic researcher with expertise in prosthetic devices and neural interfaces, and who has undergone BKA bilaterally), and MIT team member/BWH staff surgeon Carty (a physician-scientist and expert in plastic & reconstructive surgery).

Potential participants in the MIT study will receive our materials (a Letter and Information Sheet). Dr. Lisa Freed or another member of our MIT study team will meet with each potential participant individually to review the study protocol, and to have any questions answered. If the individuals decide to participate in the study, they will be asked to sign our Informed Consent Form.

3. Informed consent. *Documented informed consent must be obtained from all participants in studies that involve human subjects. You must use the templates available on the COUHES website to prepare these forms. Draft informed consent forms must be returned with this application. Under certain* ***very limited*** *circumstances, COUHES may waive the requirement for informed consent. If you are requesting a* ***waiver or alteration of consent****, please attach the Waiver or Alteration of Informed Consent Request form.*

[Attach informed consent form(s) with this application.]

4. Subject compensation. *Payment must be reasonable in relation to the time and trouble associated with participating in the study. It cannot constitute an undue inducement to participate.*

Describe all plans to pay subjects in cash or other form of payment (i.e. gift certificate)
Subjects will be paid $20 per hour for their involvement in the experiment. This may change if

necessary for recruitment. Should a subject withdraw from the study for any reason, they will be compensated for the time they did participate.

Will subjects be reimbursed for travel and expenses?
In-town travel expenses will not be reimbursed.

5. Potential risks. *A risk is a potential harm that a reasonable person would consider important in deciding whether to participate in research. Risks can be categorized as physical, psychological, sociological, economic and legal, and include pain, stress, invasion of privacy, embarrassment or exposure of sensitive or confidential data. All potential risks and discomforts must be minimized to the greatest extent possible by using e.g., appropriate monitoring, safety devices and withdrawal of a subject if there is evidence of a specific adverse event.*

What are the risks / discomforts associated with each intervention or procedure in the study?
(1) Risk of prosthetic device malfunction. Since the powered 2-DoF prosthesis is an active device, there is a risk of malfunction.
(2) Risk of skin discomfort. Since surface EMG electrodes and other wearable sensors are applied using adhesive, there is a chance of discomfort upon sensor application or removal, and a chance of leaving adhesive residue behind on the subject's skin or clothing.
(3) Risk of fall. As is the case when any person uses a prosthetic device for walking or terrain traversal, there is a risk of falling.
(4) Risk of fatigue. There is a risk of becoming fatigued during the study.
(5) Risk of muscle discomfort. There is a risk of muscle discomfort when the clinician places the fine-wire electrodes, and during the muscle stimulation study which involves the use of small, controlled bursts of electricity. Sensations associated with muscle stimulation are typically described as "tingly" and we expect you to feel your muscle contracting.
(6) Risk of infection. There is a risk of infection if fine-wire electrodes are left in place overnight.
(7) Risk of confidentiality breach. There is a risk that data confidentiality may be compromised.
What procedures will be in place to prevent / minimize potential risks or discomfort?
(1) The individuals developing the prosthesis make every effort to reduce the risk of prosthetic device malfunction. In the case that a malfunction occurs, then the prosthesis defaults from an active state to an inactive state and becomes nearly rigid and much like a standard passive ankle-foot prosthesis. Bob Emerson, a certified prosthetist who directs A Step Ahead Prosthetics in Burlington, MA, is a long-time professional colleague of the PI and will provide expert advice and assistance as needed.
(2) Subjects are given an option to wear clothing provided by the lab. Alcohol wipes are offered to help remove adhesive residue from subjects' skin or clothing.
(3) To protect against risk of falling, our lab is equipped with handrails, parallel bars and a safety harness. There will be a "spotter" standing next to the subject at all times during standing or ambulatory trials.
(4) To protect against risk of fatigue, subjects are given breaks between trials, and may ask to take a break or ask to stop at any time.
(5) To minimize muscle discomfort, an experienced clinician will place the fine-wire electrodes to mitigate the discomfort associated with this procedure. During muscle stimulation, all stimulation settings are within historically safe limits and tuned for each subject. We begin at low intensity, and slowly increase intensity until the subject tell us we have reached a limit of comfortable stimulation or until we reach the limit of what is historically safe (whichever comes first). Once we determine this limit, we set up the stimulation system to ensure that this limit is never surpassed. Participants are

instructed to let us know if they need to take a break or if they want us to remove the electrodes or stop the stimulation. Participants are instructed to let us know immediately if the muscle stimulation becomes at all painful, in which case we will stop the study.
(6) To protect against risk of infection, sterile fine-wire electrodes are placed by an experienced clinician. In the event that sessions are scheduled over two consecutive days, the fine-wire electrodes may remain in place overnight. In this scenario, the clinician applies local antibiotic ointment to the insertion points and bandages the limb. The subject is instructed not to remove the bandage, not try to use the socket or bear weight on the limb, and, in the event she/he has any problems or concerns with the electrodes overnight, that the clinician will be available by telephone. To date, there were no adverse effects of fine-wire electrode studies during COUHES protocol (1609692618-Herr), under which the experiments performed were identical to those proposed herein.
(7) To further prevent / minimize potential risks or discomfort related to the fine-wire electrode studies we will involve an independent safety monitor. Dr. Rickard Braanemark M.D., Ph.D. has agreed to being included. Dr. Braanemark is chosen for his significant clinical contribution to and expertise in the safe implementation of human-device interfaces for amputee populations. He will receive and review our progress and safety data for these studies involving fine-wire electrodes and provide the Principal Investigator, Dr. Herr, with recommendations for preventing/mitigating risks.
(8) Although efforts are made to ensure that the human subject data being collected are stored in a secure manner, and labeled using a numerical code rather than a subject's name, there is a risk that data confidentiality could be compromised. However, it is not anticipated that release of these data poses a significant risk to the subjects.

6. Potential benefits

What potential benefits may subjects receive from participating in the study?
There are no immediate benefits from participating in this study. The prosthetic device and system components we are using are prototypes and are not immediately available.

What potential benefits can society expect from the study?
The plan outlined in this study uniquely combines leading-edge technologies in surgery, wearable robotic devices, prosthetic control strategies, and device-based afferent feedback. Recent clinical developments in the fields of reconstructive surgery (e.g., targeted muscle reinnervation; regenerative peripheral nerve interfaces) and implantable devices for neuro-stimulation and recording provide evidence in support of the importance of knowledge to be gained. The technologies proposed herein are next steps toward affording prosthesis wearers new motor and sensory capabilities that can improve the health, productivity, independence, and quality of life of individuals living with limb loss. The potential benefits of this study to society outweigh the minimal risks that are involved.

7. Data collection, storage, and confidentiality

How will data be collected?
The data from the 2-DoF prosthesis, the motion-capture system, EMG electrodes, and ultrasound transducers are collected either wirelessly or non-wirelessly and securely stored on local computers in the MIT Media Lab Biomechatronics Group.

Is there audio or videotaping? YES ☒ NO ☐ ***Explain the procedures you plan to follow.***
We record photographs, videotapes, and audiotapes in digital format for analysis and development purposes. These data will be stored on password-protected computers in the MIT Media Lab

Biomechatronics Group and in the MIT Media Lab network hub folder, which is managed by the Media Lab IT department and individually password-protected. Access to these materials is limited to IRB-trained investigators associated with this study. If photos, video, audio or video data are published, reported, or used for educational purposes, subject identity will be protected or disguised by blurring or blocking the face. If any other uses of these data are contemplated, subjects will be contacted by phone, mail or Email requesting specific their consent from to do so.

Will data be associated with personal identifiers or will it be coded?

Personal identifiers ☐ **Coded** ☒ ***Explain the procedures you plan to follow.***
All data and files particular to a subject will be anonymized (each subject will be assigned a numerical code for naming files e.g. subject1_month_day_year). Only the Principal Investigator (Dr. Herr) and Key Personnel (Dr. Freed and Dr. Carty) will have access to the coded data linking the subjects' names with their numbers. These individuals will store the code, separately from the data itself, on password-protected computers in the MIT Media Lab Biomechatronics Group.

Where will the data be stored and how will it be secured?
Study data will be stored on password-protected computers in the MIT Media Lab Biomechatronics Group (MIT E14-274 and E15-463). Study data will also be stored in the MIT Media Lab network hub folder, which is managed by the Media Lab IT department and individually password-protected. Only Biomechatronics group MIT personnel with valid IRB training certificates will have access to this folder. Individuals who no longer have valid IRB certificates, or who leave the group, will no longer be granted access this folder.

What will happen to the data when the study is completed?
The data will remain in the MIT Media Laboratory network secure server for processing and reference. Upon subject request, digital photos and videos can deleted from the data server once study is completed. The code linking subjects' names with their numbers will remain accessible only to the Principal Investigator. If results of the research are published or reported, no information will be included that can reveal the subject's identity. If used in reports, publications, or for other educational purposes, the data will not include any information that could reveal a subject's identity. If videos photos are used in reports, publications, or for other educational purposes, subject identity will be protected. If any other uses of these data are contemplated, subjects will be contacted by phone, mail or Email requesting their specific consent to do so.

Can data acquired in the study affect a subject's relationship with other individuals (e.g. employee-supervisor, patient — physician, student-teacher, family relationships)?
No

8. Deception *Investigators must not exclude information from a subject that a reasonable person would want to know in deciding whether to participate in a study.*

Will information about the research purpose and design be withheld from subjects?
YES ☐ **NO** ☒

If YES, explain and justify. Not Applicable

9. Adverse effects. *Serious or unexpected adverse reactions or injuries, and/or unanticipated problems involving risks to subjects or others must be reported to COUHES within 48 hours. Other adverse events should be reported within 10 working days.*

What follow-up efforts will be made to detect any harm to subjects, and how will COUHES be kept informed?

Contact information for the Principal Investigator and Key Personnel will be provided to the subjects for the purpose of reporting any adverse effect or injury. These study personnel will report any adverse events to COUHES within the required time frames.

10. Health Insurance Portability and Accountability Act ("HIPAA"). *If your study (i) involves individually identifiable health information and (ii) is sponsored by MIT Medical, an MIT Health Plan or another healthcare provider, then you must complete the questions below because HIPAA likely applies to your study. For more information regarding the applicability of HIPAA to human subjects research, please click here.*

Do you plan to obtain, use or disclose identifiable health information in connection with your research study?

YES ☐ **NO** ☒

If YES, then all participants must complete an Authorization for Release of Protected Health Information Form. Please attach a copy of this draft form. You must use the template available on the COUHES website.

*Alternatively, COUHES may grant a Waiver of Authorization in certain **very limited** circumstances when use of individually identifiable health information would pose only minimal risk to study participants (among other requirements). For additional information regarding whether your study might qualify for a waiver, please click here.*

Are you requesting a Waiver of Authorization?

YES ☐ **NO** ☒

If YES, explain your rationale for concluding that: (i) use of participant health information poses no more than minimal risk; (ii) the research could not be conducted without the waiver and (iii) the research could not be conducted without the information. In addition, please explain your plan for (i) ensuring the participant health information is not improperly used or disclosed either within MIT or to any outside third parties and (ii) destroying identifiers at the earliest possible opportunity.

Will the health information you will receive for use in this study be de-identified?

YES ☒ **NO** ☐

If YES, you do not need to obtain a signed Authorization for Release of Protected Health Information Form from study participants. Note, however, that if you receive identifiable participant health information that you plan to convert into de-identified information for use by other researchers, then you must obtain a signed Authorization for Release of Protected Health Information Form from each participant before receiving their identifiable health information for use in your study.

Will you be using or disclosing a limited data set?
YES ☐ NO ☒

If YES, and you will only receive participant health information in limited data set form, then you do not need to obtain a signed Authorization for Release of Protected Health Information Form from study participants. You must complete a formal data use agreement with the party from whom you will receive the limited data set information in order for your application to be approved.

If YES, and you will receive identifiable participant health information that you plan to convert into limited data set form for use by other researchers, then you must obtain a signed Authorization for Release of Protected Health Information Form from each participant before receiving their identifiable health information for use in your study. You must complete a formal data use agreement in order for your application to be approved.

V. INVESTIGATOR'S ASSURANCE

I certify the information provided in this application is complete and correct.

I understand that I have ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by COUHES

I agree to comply with all MIT policies, as well all federal, state and local laws on the protection of human subjects in research, including:

- **ensuring all study personnel satisfactorily complete human subjects training;**
- **performing the study according to the approved protocol;**
- **implementing no changes in the approved study without COUHES approval;**
- **obtaining informed consent from subjects using only the currently approved consent form;**
- **protecting identifiable health information, to the extent required by law, in accordance with HIPAA requirements; and**
- **promptly reporting significant or untoward adverse effects.**

Signature of Principal Investigator _____ **Date** _____

Print Full Name and Title _____

Signature of Department Head _____ **Date** _____

Print Full Name and Title _____

By signing this form you confirm a scientific review of the proposed research has been conducted, and that the proposed research is of scientific and scholarly validity.

The electronic file should be sent as an attachment to an e-mail: couhes@mit.edu. In addition, two single sided hard copies (one with original signatures) should be sent to the COUHES office: Building E25-Room 143B.

	Massachusetts Institute of Technology Committee on the Use of Humans as Experimental Subjects	**Protocol #** (assigned by COUHES)	

PERSONNEL LIST

This form must be attached to both standard and exempt form applications. ***Any application submitted without a completed personnel list will be returned to you.***

Personnel is defined as anyone who plays a role in research involving human subjects, including direct contact, indirect involvement, analysis of data, blood or tissue samples. This extends to principal investigators, associate investigators, student investigators, study coordinators, visiting scientists, consultants, laboratory technicians and assistants.

All study personnel must be listed below. This listing must include contact information, a brief statement of qualifications and their study role.

Important note: all study personnel are required to complete Human Subject Training before work begins on the project. Proof of training must be attached for non-affiliates. (Documentation from collaborating institutions may be submitted in lieu of training certificates.)

A. MIT AFFILIATES

Personnel name, and e-mail address	*Qualifications: Describe briefly*	*Study role(s):*	*Check if obtaining consent*
Contact* [redacted]	PhD in Mechanical Engineering, Distinguished Postdoctoral Fellow	Key personnel, serves as contact person, prepares NIH reports, assists in overall research	☐
[redacted]	PhD, Professor, MIT Media Lab Biomechatronics Group Director	Principal Investigator. Oversees all research activities and ensures that all research is properly conducted	☒
[redacted]	MD, MIT Visiting Scientist, Staff Surgeon, BWH and Faulkner Hospitals; & HMS Associate Professor of Surgery	Key Personnel. Places the fine-wire electrodes and takes part in all research activities	☒
[redacted]	PhD Candidate, MIT-MAS	Assists in conducting research	☐

[redacted]	PhD Candidate, MIT-MAS	Assists in conducting research	☒
[redacted]	PhD Candidate, MIT-MAS	Assists in conducting research	☒
[redacted]	MD, a Surgeon at the Massachusetts General Hospital	Places fine-wire electrodes and takes part in all research activities.	☒
[redacted]	Postdoctoral Associate	Assists in conducting research	☒
[redacted]	SM Student, MIT-MAS	Assists in conducting research	☒
[redacted]	SM Candidate	Assists in conducting research	☐
[redacted]	MD Clinician at MGH	Clinician and research affiliate, place the fine-wire electrodes, and take part in all research activities	☐
[redacted]	MD Clinician at MGH	Clinician and research affiliate, place the fine-wire electrodes, and take part in all research activities	☐

***NOTE:** Please designate a person with whom COUHES should communicate regarding issues or questions about the protocol.

B. NON-MIT AFFILIATES

Name, affiliation, and e-mail address	*Qualifications: Describe briefly*	*Study role(s):*	*Check if obtaining consent*	*Check if human subject training has been completed*
Name: Email:			☐	☐
Name: Email:			☐	☐
Name: Email:			☐	☐
Name: Email:			☐	☐