Project Title

Restoring High Dimensional Hand Function to Persons With Chronic High Tetraplegia

NCT Number

NCT03482310

Document Date

Approved March 23, 2018

IRB #: 18013-HO6
(Assigned by IRB Office)

Approved
3/23/18
Cleveland VAMC
Institutional Review Board

CPA #: 7894
(Assigned by IRB Office)

***Form Directions**: Form is protected (user has limited access to the fill-in fields). Use the tab key or mouse to navigate the fill-in fields. Formatting is limited in the text fields (no bulleted lists, numbering, etc). In the event that the user is unable to navigate through the protected document or would like to format a document, the user can disable the "protected" feature (select "Review" then "Restrict Ending" then "Stop Protection"). Please do not delete or modify questions..*

Louis Stokes Cleveland Department of Veterans Affairs Medical Center Research Plan

Please contact the IRB office if you have any questions at (216) 791-3800 ext. 4658.

☐ **Request for Expedited IRB Review Form attached**

Human Subject Research: Human subject research means research involving interaction or intervention with living human beings or access to identifiable private information of living human beings.

Research Plan: The information requested in the Research Plan is designed to provide the IRB with the necessary information such that it can make the federally required determinations codified at 38 CFR Part 16, 21 CFR Parts 50, 54, & 56, and 45 CFR Part 46

The **Research Plan** is to be written so that the non-scientist/non-medical members of the IRB can understand the research proposed. Define all abbreviations and terms that are not part of common language.

Version Date: This should be updated subsequently with every modification to any part of the Research Plan. Any modification to this document, no matter how minor, must be reviewed and approved by the IRB prior to implementation. The Research Plan will be stamped with the date of IRB approval

Section 1 – General Information

1. **Version Date:** 03/23/2018

2. **Title of Project:** Restoring Control of Multi-Dimensional Upper Limb Function in People with High Tetraplegia

3. **Principal Investigator (PI)** *(name & degrees)*: A. Bolu Ajiboye, PhD

   E-mail: aba20@case.edu

   Pager Number/Cell Phone Number: 216-368-6814

4. **Research Contact/Research Coordinator** *(name, degrees)*: **William Memberg, M.S.**

   E-mail: wdm@case.edu

   Pager Number/Cell Phone Number: 330-416-5477

Section 2 – Research Sites and Sponsor

5. Please list all Research Sites in addition to Louis Stokes Cleveland DVA Medical Center (LSCDVAMC);

International studies when the PI is the Lead Investigator list the countries: N/A

a. When study procedures including analysis of identifiable samples or data involving LSCDVAMC enrolled subjects will be conducted at any site other than the LSCDVAMC please provide the following:

Name and contact information for the site: Providence VA Medical Center; Leigh Hochberg, MD

Describe the plan for communicating protocol amendments, reports of serious adverse events, reports of unanticipated problems involving risks to subjects or others, interim reports, and DSMB reports to external sites. These items will be discussed as part of the existing biweekly conference call among the BrainGate Principal Investigators.

*** When the LSCDVAMC is considered the coordinating center and the PI the lead investigator on cooperative research or a multi-center trial contact AO/Research Holly.Henry@va.gov.**

6. Sponsor or other Support *(list industry sponsor, government support, etc.)*:

VA-ORD

Section 3 – Research Design and Procedures

7. Definitions- Provide a list of all abbreviations and specialized terms to be used in this document and their definitions:

Abbreviations / Specialized Terms *(Use the Enter key in this column to insert additional abbreviations and their definitions)*	**Definition**
LSCDVAMC	Louis Stokes Cleveland DVA Medical Center
FES	Functional Electrical Stimulation
BCI	Brain Computer Interface
HT	High Tetraplegia
SCI	Spinal Cord Injury

8. Provide a BRIEF SUMMARY of the background for this research. DO NOT CUT and PASTE paragraphs that do NOT summarize the background.

- *Include a critical evaluation of existing knowledge, and specifically identify the information gaps that your protocol is intended to fill.*

- *Refer to appropriate citations in the scientific literature and include your references at the end of this section.*
- *Include the rationale for conducting the research at the VA.*

Spinal cord injury (SCI) resulting in paralysis affects over 250,000 people nationwide with over 12,000 new cases each year. Slightly more than half of all SCI cases occur at cervical levels (tetraplegia). Incomplete and complete tetraplegia have accounted respectively for 34% and 18% of all SCI cases since 2000, with less than 1% of all cases achieving full recovery [1]. Veterans comprise almost 20% of SCI patients [2]. Even with a caregiver, many of these individuals experience a lower quality of life due to loss of personal independence from the inability to perform standard activities-of-daily-living (ADL) on their own, such as grasping objects for drinking and self-feeding.

Veterans and others with low cervical SCI (C5-C7) resulting in chronic hand paralysis can regain grasp function through electromyogram (EMG i.e. muscle) commanded functional electrical stimulation (FES) neuroprostheses. However, Veterans and others with high cervical SCI (C1-C4) resulting in chronic tetraplegia have limited to no voluntary EMG function post-injury to use as a command source, and hence cannot adequately use current FES grasp prostheses. FES grasp prostheses restore the ability to cycle between two hand grasps, whereas able-bodied persons use at least six different hand grasps [3-5], in addition to individuated finger movements, when interacting with everyday objects. This discrepancy implies that even for Veterans who have the option of using current FES grasp prostheses, there are many tasks involving the hand that they could not do easily, or possibly at all. For FES grasp prostheses to approach the dexterity of able-bodied grasping, and to be relevant to persons with C1-C4 SCI, fundamental advances are needed in 1) how grasp function is implemented, and 2) the command source used. The present study thus aims to investigate novel methods and interfaces for providing highly dexterous hand and arm function to Veterans and others primarily with high cervical SCI, with applicability to Veterans and others with low cervical SCI and other injuries resulting in hand and arm movement impairment.

The range of functional tasks that people perform on a daily basis requires varying hand grasps and movements for successful completion. For example, buttoning one's shirt requires the ability to perform a precision grasp where the thumb and index finger finely grasp and manipulate the button and slip. Dexterous and coordinated manipulation of the thumb, index, and middle-ring-pinky (T-I-MRP) fingers is required to accurately and safely use a pair of scissors. Using forks and spoons for self-feeding requires a whole hand lateral grasp (thumb pad opposes lateral phalanx of index finger), while using a writing utensil requires a whole hand palmar grasp (thumb tip opposes tips of index and middle fingers). Even the fairly simple act of picking up a pencil from a table and positioning it correctly for writing is extremely difficult if the user is limited to the standard palmar and lateral grasps implemented in current hand grasp prostheses and cannot perform basic finger manipulations (users end up putting the pencil in their mouth to make positioning adjustments). Thus, the wide range of tasks that people typically to do on their own requires the ability to use traditional whole hand grasp categories (e.g. lateral, palmar) and more dexterous individuated finger manipulations. Current arm/hand neuroprostheses available to persons with chronic tetraplegia implement two hand grasp options, using an effective but non-optimal menu selection scheme. To increase the independence of Veterans and others with chronic paralysis who aim to use arm and hand neuroprosthetic restorative technologies, we must investigate methods for enhancing dexterity of existing arm/hand neuroprostheses, and specifically how to 1) increase the number of available hand grasps, 2) increase the independent movements of the thumb and index finger in these neuroprostheses, and 3) enhance the ability of users to more easily command the dexterity of these higher dimensional arm/hand neuroprostheses.

Intracortical brain-computer interfaces (iBCIs) are a novel technology for converting brain activity into command of external devices. Human participants have demonstrated the ability to use iBCIs to

command the three dimensional movements of a robotic arm to pick up and drink from a cup [6], as well as perform dexterous robotic hand manipulations [7-8]. Recently, investigators have demonstrated that a human implanted with an iBCI could command up to ten dimensions of a robotic arm and hand, to pick up and transport selected objects [9]. Recently, investigators at Case Western Reserve University have demonstrated a person with chronic paralysis commanding the single-joint movements of his own paralyzed arm and hand, powered by FES, using an iBCI [10]. The participant used this FES+iBCI system to grasp and drink from a cup of coffee, and hold a fork and feed himself from a bowl of mashed potatoes. The present study aims to advance the clinical viability and dexterity of these system using two implementation methods for dexterous hand grasping and continuous arm movements An iBCI will be used as the command source to expand grasp functionality and arm movements and ultimately independence in persons with chronic and severe paralysis. iBCIs may offer to persons with C1-C4 SCI a viable means of commanding the high dimensional hand and arm functions required for increased reaching and grasp functionality. Persons with paralysis are highly amenable to receiving iBCIs, provided that the functional gain is significant over less invasive command sources [11-13]. Success of the present proposal will thus establish novel methods for restoring high-dimensional hand grasp and arm reaching function for Veterans and others with chronic paralysis, and quantitatively compare an FES+iBCI hand neuroprosthesis with currently available FES+EMG grasp prostheses in functional assessment tasks.

REFERENCES

[1] NSCISC. Spinal cord injury. Facts and figures at a glance. J. Spinal Cord Med. 36, 1–2 (2013).

[2] VA. VA and Spinal Cord Injury: Fact Sheet. (2007).

[3] Kamakura, N., Matsuo, M., Ishii, H., Mitsuboshi, F. & Miura, Y. Patterns of static prehension in normal hands. Am. J. Occup. Ther. 34, 437–445 (1980).

[4] Ajiboye, A. B, & Weir, R. F. Fuzzy C-means clustering analysis of the EMG patterns of six major hand grasps. Proc. 2005 IEEE 9th Int. Conf. Rehabil. Robot. 2005, 49–52 (2005).

[5] Birdwell, J. A., Hargrove, L. J., Weir, R. F. & Kuiken, T. A. Extrinsic finger and thumb muscles command a virtual hand to allow individual finger and grasp control. IEEE Trans. Biomed. Eng. 62, 218–226 (2015).

[6] Hochberg, L. R. et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature 442, 164–171 (2006).

[7] Collinger, J. L. et al. High-performance neuroprosthetic control by an individual with tetraplegia. Lancet 381, 557–564 (2013).

[8] Collinger, J. L. et al. Collaborative Approach in the Development of High-Performance Brain-Computer Interfaces for a Neuroprosthetic Arm: Translation from Animal Models to Human Control. Clin. Transl. Sci. 7, 52–59 (2013).

[9] Wodlinger, B. et al. Ten-dimensional anthropomorphic arm control in a human brain − machine interface: difficulties, solutions, and limitations. J Neural Eng 12, (2015).

[10] Ajiboye, A. B. et al. Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia : a proof-of-concept demonstration. Lancet 6736, (2017).

[11] Blabe, C. H. et al. Assessment of brain–machine interfaces from the perspective of people with paralysis. J. Neural Eng. 12, 43002 (2015).

[12] Lahr, J. et al. Invasive brain–machine interfaces: a survey of paralyzed patients' attitudes, knowledge and methods of information retrieval. J. Neural Eng. 12, 43001 (2015).

[13] Collinger, J. L. et al. Functional Priorities, Assistive Technology, and Brain-Computer Interfaces after Spinal Cord Injury. J Rehabil Res Dev 50, 145–160 (2013).

9. Provide a BRIEF SUMMARY of the purpose and scientific rationale for this research. DO NOT CUT and PASTE paragraphs that do NOT summarize the purpose and scientific rationale.

- *State clearly, in terms a non-scientist/non-medical person can comprehend, what you expect to learn from the study and the specific hypothesis (es) to be tested.*
- *The objectives should be stated in such a way that the reader can determine the appropriateness of the study design.*

This work aims to advance Brain-Computer-Interfaces (BCIs) to provide severely paralyzed persons a natural way of controlling Functional Electrical Stimulation (FES) neuroprostheses for restoring arm and dexterous hand movements. The prospect of using BCI technology for restoring arm and hand movements for reaching and grasping is based on the hypothesis that in a paralyzed human, there is a repeatable and understandable relationship between recordable brain activity and specific aspects of imagined arm movements. Many previous studies have attempted to understand the relationships between brain activity and arm and hand movements in able-bodied monkeys. Little is known about these same relationships in humans, and specifically within the context of trying to control an FES arm and complex hand system. This study will recruit persons who already have BCI and FES systems implanted to take advantage of the possibility of recording high resolution brain activity in human participants. Thus, from this study, we aim to gain a better understanding of how brain signals are related to specific aspects of arm and complex hand movements in humans with paralysis. Additionally, this study will test novel implementations of complex hand movement restoration in Veterans and other persons with chronic hand and arm paralysis.

10. Describe the means of analyzing the data and evaluating the results.

- *State the anticipated methods to be used for analysis and interpretation of the data.*
- *The methods must compliment the design of the study and the nature of the data which is being collected.*

From the recorded brain activity, the data analysis will consist of developing mathematical models which attempt to correlate the brain activity to movement parameters of the hand (e.g. finger angles, and whole hand states). We will investigate several different correlation models, which focus on extracting information from different aspects (i.e. features and/or frequencies) of the neural activity. We will use correlation models based upon linear regression, neural networks, and system identification. We will test these models under a variety of scenarios, including varying levels of signal variation and noise. The analysis will result in correlation models that will be assessed by how well they are able to predict the hand states and continuous arm and finger movements required for grasping function. The metric of efficacy will be the Variance Accounted For (%VAF), which is qualitatively similar to an r-squared metric. Effectively the correlation models are determining statistical (linear or nonlinear) fits of the neural data (input) to the desired hand movements (outputs). The returned p-values of these fits will assess if the models produce statistically significant correct predictions. The final result of these analyses will be one or more models that study participants will then use in a real-time application, using direct cortical signals, to control hand states and and arm and finger movements of their own FES arm and hand.

11. Provide a BRIEF DESCRIPTION of how the estimated number of study subjects needed for this research was determined

- *If this is a quantitative study provide the method of determining sample size estimates.*
- *If multiple studies are planned provide a power analysis or justification for each one.*

This nature of this study is exploratory in nature (rather than quantitative) in that we aim to better understand how hand function is encoded in cortical signals, and then use this understanding to develop corrleation models for real-time control of an FES neuroprosthesis. We need to tweak several parameters of each model based upon experimental data, and then test the optimized models in actual control experiments. Consequently the number of required subjects is not elucidated by a standard statistical power analysis. The present study does aim to enroll up to four persons with paralysis (C1-C4 SCI, resulting in complete tetraplegia) who already have intracortical brain arrays and FES systems implanted. The study leverages the clinical and recruiting efforts of the separately funded Braingate2 Clinical Trial in Cleveland that recruits persons with C1-C4 SCI to receive BCI and FES systems.

12. The research involves the following procedures conducted by and for what purpose:

PROCEDURE	PERFORMED BY:		PROCEDURE IS:	
	Research Staff	LSCDVAMC Clinical or Support Staff	Standard of Care*	For Research Purposes Only**
Audiotaping / Videotaping *Attach VA Form 10-3203* **REQUIRED ONLY FOR IN-PATIENT AND OUT-PATIENT SUBJECTS**	☒	☐	☐	☒
Biopsy	☐	☐	☐	☐
Blood collection	☐	☐	☐	☐
Chart review – prospective	☐	☐	☐	☐
Chart review – retrospective	☐	☐	☐	☐
Review of existing data (ex: registry, Database , etc.)	☐	☐	☐	☐
X-ray or Ionizing radiation exposure	☐	☐	☐	☐
Clinical Tests	☐	☐	☐	☐
Device implantation	☐	☐	☐	☐
Drug administration	☐	☐	☐	☐
EEG, EKG , ECG...etc	☒	☐	☐	☒
Gene therapy, Genetic analysis	☐	☐	☐	☐
Pregnancy/Breastfeeding Screening	☐	☐	☐	☐

PROCEDURE	PERFORMED BY:		PROCEDURE IS:	
	Research Staff	LSCDVAMC Clinical or Support Staff	Standard of Care*	For Research Purposes Only**
Interview, Questionnaire, Diary, Survey *(please attach)*	☐	☐	☐	☐
Stool collection, Urine collection, or any Non-surgical Specimen collection	☐	☐	☐	☐
Surgical procedure or Specimen removal during surgery	☐	☐	☐	☐
Tissue banking *(complete Section 12)*	☐	☐	☐	☐
Use of pre-existing tissues/specimens	☐	☐	☐	☐
Other *(list)*: EMG	☒	☐	☐	☒

- **Standard of care procedures are procedures performed in the course of normal medical care.*
- ***Research Procedures are performed for the purposes of this research alone.*

13. Please describe the research design and all study related procedures.

- *Describe **ALL PROCEDURES ASSOCIATED WITH THIS RESEARCH**. This includes standard of care and research procedures.*
- *For complex studies please include diagrams and tables. Be sure to describe when each procedure will be performed. Be sure to provide information for **each cohort, including normal controls**).*

All study participants will have already had implanted one or two 96-channel microelectrode arrays in the primary motor cortex (M1), as well as stimulating electrodes for restoration of hand and arm function via FES.

Study participants will be instructed to imagine and attempt to perform various virtual finger, hand, and arm movements on a computer screen. Participants will be seated in front of a 3D monitor and observe a virtual arm/hand perform the movements. If needed to help perceive the 3D animation, the participant may wear stereoscopic glasses. Neural activity, sampled at 30 kHz, will be recorded during this motor imagery exercise. Offline, we will use standard discriminant algorithms, including linear discriminant analysis (LDA), and support vector machines (SVM), to investigate how well separated the movement patterns are based upon the neural activity alone. Participants will then use the best of these algorithms to perform a virtual "closed-loop" task. Similar to the above study, participants will be instructed to imagine and attempt to perform various hand and arm movements as presented on the computer screen. As the user imagines these movements, the recorded brain activity will be converted in real-time, through the algorithm, into movements of the virtual arm and hand. When the brain-controlled movements match the instructed movements, the participant will receive a cue indicating success. The participants will perform several trials of this task to assess how well they can perform this brain control of hand and arm movements and how well the algorithms decode their intended movements.

Participants will also attempt to command movements of their paralyzed limb reanimated through functional electrical stimulation (FES). They will first do so using the iBCI and optimized algorithm that converts brain activity into a desired movement command. The desired movement command will be converted into electrical stimulation patterns that will be applied to the paralyzed muscles. A low frequency electrical stimulus will be sent to each appropriate muscle to cause it to contract and move as the participant has mentally instructed. The participants will attempt to use his brain-controlled paralyzed arm to perform a series of standard clinical tasks where they are required to pick up and move objects from point A to point B. Participants will also attempt to perform these same clinical tasks using standard electromyography (EMG) signals to command the paralyzed arm and hand, to compare to the performance of the brain control. Surface electrodes for recording muscle activity will be placed on muscles still under voluntary control, such as the platysma (neck) and aricularis (ear) muscles. When participants contract these muscles, EMG signals will be differentially recorded, filtered (10-1000 Hz), amplified, sampled, and smoothed at 20 Hz to produce the EMG envelope as a command signal. This command signal will then control the stimulation of the desired paralyzed muscles, and hence the movements of the paralyzed but reanimated arm and hand. This implementation is comparable to current EMG controlled FES systems, and performance using this approach will be compared to performance using the brain interface approach.

14. Will the research involve the following?

☐ **N/A** **Chart/Data Review**

Placebo Group	☒ **No**	☐ **Yes** *(describe)*:
Other Control Group	☒ **No**	☐ **Yes** *(describe)*:
Randomization	☒ **No**	☐ **Yes** *(describe)*:
Deception	☒ **No**	☐ **Yes** *(describe)*:

15. Does the research involve the use and/or disclosure of Individually Identifiable Health Information in any form or medium?

☐ **No** ☒ **Yes** **If yes, complete the required HIPAA Waiver/Authorization forms.**

16. Does the study include the administration of a study agent that does not require FDA approval and does not require an IND (e.g. vitamins, food supplements, isotope tracers, alternative medicines, etc.)?

☒ **No** ☐ **Yes** *-provide a detailed description of the procedures used to assure patient safety:*

17. Will radioactive material be administered or will subjects be exposed to ionizing radiation?

- *Ex. Radiographic equipment, fluoroscopic equipment, and CT scanners, etc.*

☒ **No** ☐ **Yes**

18. In your judgment, could the objectives of the research be met in a way that presents less risk to subjects?

☒ **No** ☐ **Yes** *please explain*:

Section 4 – Subject Selection, Recruitment, and Vulnerable Populations

19. Anticipated duration of entire study reported in years: 4

20. Estimated number of subjects to be studied at the LSCDVAMC or charts/records to be reviewed.

- *Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,)*:

4 participants

21. Estimated number of subjects to be studied or charts/records to be reviewed at all sites

- *Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,)*

6 (4 in Cleveland, 2 in Providence)

N/A SINGLE SITE ☐

22. Duration of individual subject participation

*Provide answers for **each cohort** including normal controls; (patients, family members, treating physicians,).* Each experimental session lasts about 4 hours. Participants will take part in 1-3 sessions per week for up to 30 sessions, which may be take up to one year.

Chart/record review ☐ **N/A**

23. Age range of subjects

- *provide answers for **each cohort**, including normal controls*:

☒ **Adults 18 years or greater**

☐ **Specific age range** (list age range):

☐ **Children –waiver from VACO:** ☐ **attached** ☐ **pending-** ***provide submission date:***

***Contact AO/Research holly.henry@va.gov for guidance..*

24. Which of the following will be recruited or reviewed for this study *(check all that apply)*?

☒ **Veteran Inpatients**
☒ **Veteran Outpatients**
☐ **Veteran Families**
☐ ***Normal volunteers**
☒ ***Non-Veterans; Provide justification The investigated population (people with high spinal cord injury without significant comorbidities) is too small to limit the study and**

☒ **Men**
☒ **Women**

recruitment to just Veterans. Additionally, all persons will spinal cord injury could stand to benefit from the study.

*According to VHA Handbook 1605.04 Notice of Privacy Practices VHA must provide a copy of its VHA Notice of Privacy Practices to all non-Veteran patients (e.g., active duty personnel or those seeking care in humanitarian circumstances) receiving care or treatment at a VHA health care facility or non-Veteran research subjects enrolled in an approved VHA research study with clinical trials. VA Form 10-0483 Acknowledgement of the Notice of Privacy Practices should be signed by the non-Veteran research subject at the time of consent and given a copy of the Notice of Privacy Practices. Once the Acknowledgement Form is signed please send a copy to the Privacy Officer. If additional information is needed please contact your Facility Privacy Officers Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / phone 8214101.

25. Which vulnerable population(s) will be TARGETED for recruitment in this study:

- *Indicate only those populations that are specifically targeted for the research described in this document.*
- ***It is not necessary to check any box if, for example, your study will include a full range of subjects, some of whom may be elderly or subjects who might incidentally be employees.***

☐ **N/A Chart Review** (*proceed to Item 30*)

☐ **NONE** (*proceed to Item 26)*

☐ **Medical students, house staff, or Employees of the VAMC or Case**

☐ **Pregnant Women OR Women who are Breastfeeding, Human Fetuses, or Neonates**

☐ **Children – Complete Section 14 "Children as Research Subjects"**

☐ **Prisoners (The LSCDVAMC does not conduct research involving prisoners)**

☐ **Targeting Persons over Age 65**

☐ **Persons with Acute/Severe Mental/Physical Disabilities** *(describe)*:

☐ **Persons with Cognitive, Social, Economic, or Educational Disadvantages** *(describe)*:

☒ **Others** *(describe)*: Existing participants in the BrainGate study may feel an obligation to enroll in this study

a. Provide the Scientific and Ethical reasons for Targeting these vulnerable populations in the research:

The study by design specifically investigates the use of neurprostheses in persons with chronic paralysis due to cervical spinal cord injury who are enrolled in the BrainGate study This is necessary to study the neural signals from their motor cortex.

b. What additional safeguards or provisions will be used to protect the rights and welfare of the identified targeted vulnerable subjects?

☐ **Surrogate consent**

☐ **Subject assent**

☐ **Use of a consent or Medical monitor**

☐ **Use of a waiting period**

☐ **A patient advocate will participate in the informed consent process**

☒ **Key elements of informed consent will be presented orally**

☐ **No supervisor or rater will be involved in obtaining consent**

☒ **Other - Describe Additional safeguards you plan to use:** The consent form will clearly explain that medical care will not be affected by a decision to participate (or not) in the research.

c. Describe the procedures used to ensure that the subject's legally authorized representative is well informed regarding his/her role and obligation to protect persons with impaired decision making capacity:

We won't be enrolling persons with impaired decision making capacity.

26. Procedures for Recruiting Subjects -check all that apply and attach all recruitment materials:

☐ **Not Applicable**

☐ **Materials; Recruitment Letter, Posting on Bulletin Board, Brochure, Flyer, Post card, etc.**

☐ **Media; Internet Ads, Press Releases, Newspaper, Radio**

☐ **Investigator's Patient Population**

☐ **Physician Referral**

☐ **Letters to Physicians/Clinicians**

☒ **Other** *(describe)*: Subjects will be recruited from participants in the BrainGate2 clinical trial

27. Will VA computer systems be used to identify potential subjects?

- *e.g. VISTA, CPRS, Pharmacy Databases, other clinical databases, etc,*

☒ **No** ☐ **Yes- Describe how the computer will be used to identify patients. List all systems used and all information to be collected:**

28. Will subjects be identified and/or recruited in clinics and/or inpatient wards at the LSDCVAMC?

☒ No ☐ Yes- **explicitly describe your process for identifying and/or recruiting these patients:** *(address all cohorts):*

29. In addition to the consent form will any other materials be given to the subject?

☐ **N/A Chart/data review**

☐ **No** ☒ **Yes- check all that apply and submit for IRB review:**

- ☐ **Letter**
- ☐ **Information Sheets**
- ☐ **Questionnaire, Survey, Diary**
- ☒ **Other** *(flyer, brochure, describe):* Photo/video consent form

30. Please list by bullet point inclusion/exclusion criteria for the study.

- *Entry criteria should be as detailed as necessary to define the subject population(s) under study and reduce confounding design. Include precise criteria for age, gender, and other relevant factors.*

- *List specific exclusion criteria which could interfere with the study design or place a subject at risk during the study.*

- *Provide answers for **each cohort**, including normal controls.*

Inclusion criteria:

- Cognitively intact (able to follow instructions)

- A spinal cord injury resulting in at least partial arm paralysis

- Participant in BrainGate2 clinical trial, having already received an intracortical array and demonstrated the ability to use the neural signals to control a cursor on a monitor.

Exclusion criteria:

- Profound visual impairments

- Participant in BrainGate2 clinical trial with insufficient recordable neural signals (such that the researchers cannot decode a movement intention command signal)

☐ **N/A Chart/data review**

31. By role, (PI, Coordinator, etc.) who will assess for eligibility and how will this be accomplished?

Eligibility for the study will be assessed by the principal investigator in consultation with the co-investigator and coordinator.

32. Are any subjects excluded on the basis of race, ethnic group, understanding of English, socioeconomic status, education, gender, or pregnancy?

- *Note: It is appropriate to indicate that you do not anticipate encountering potential subjects who do not speak English **based on the population to be studied***

☐ **No** ☒ **Yes** - *(provide justification)*: Non-English speaking subjects will be excluded, since they will need to understand English instructions during the testing sessions.

☐ **N/A Chart/data review**

33. Will subjects be reimbursed or paid an incentive for participating?

☒ **No (skip to item #35)** ☐ **Yes**

☐ **N/A Chart/data review (skip to item #38)**

34. How and when will they be paid?

☐ **Cash** ☐ **Check** ☐ **Other** -please explain:

☐ **Prorated** -provide schedule: ☐ **Fixed** -provide schedule

35. Will subjects be responsible for any of the costs related to the research?

☒ **No** ☐ **Yes**- please explain:

36. Will treating physicians, clinicians, or researchers be compensated or paid an incentive for referring or enrolling subjects?

☒ **No** ☐ **Yes** -please explain:

37. Please describe steps you will take to ensure that subject selection is fair and equitable:

Potential subjects who are already participating in the BrainGate study will be reviewed and discussed by the research team. BrainGate participants are recruited from underrepresented groups in approximately the same proportions as in the population of Northeast Ohio. Since a majority of spinal cord injured individuals are male, we expect to recruit more males than females for this study.

Section 5 – Risks and Benefits

38. Please list by bullet and describe the reasonably foreseeable physical, psychological, social, economic, and privacy risks, side effects, or discomforts associated with the research and their expected frequency and severity.

- *If this study is a retrospective chart review, or involves only the analysis of data, risk may still be present in the form of data security concerns.*

Risks related to connecting to the Brain Computer Interface (BCI):

- To record brain activity, we need to connect a cable to the BrainGate2 pedestals that are mounted to the participant's skull. The standard BrainGate2 clinical trial connection methods will be followed, which involve the following risks:

- Mechanical damage to the pedestal connector. Very rare occurrence, moderate severity.

- Infection of the tissue around the pedestal connector. Rare occurrence, moderate severity.

- Electrical safety - there is a possibility of a shock hazard, including an electrical burn, whenever electricity is used within or near the body. There is a possibility of electrical burns from the external electronic devices utilized with the BrainGate2 recording equipment. Very rare occurrence, moderate severity.

Risks related to connecting to the FES arm and hand electrodes:

- Skin Irritations - Tape used to hold down the external cables may cause skin irritation. Rare occurrence, mild severity

- Electrical safety - There is a possibility of a shock hazard, including an electrical burn, whenever electricity is used within or near the body. There is a possibility of electrical burns from the external electronic devices utilized with the FES system. Very rare occurrence, moderate severity.

Risks related to the surface EMG recording electrodes:

- Skin Irritations - Tape and adhesives used in surface electrodes may cause skin irritation. Occasional occurrence, mild severity

- Electrical safety - There is a possibility of a shock hazard, including an electrical burn, whenever electricity is used within or near the body. There is a possibility of electrical burns from the external electronic devices utilized with the EMG recording system. Very rare occurrence, moderate severity.

Data security risks

- Risk of privacy breach allowing identifiable health information to be disclosed. Rare occurrence, mild severity.

***Certificate of Confidentiality:**

- Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure.
- They allow the investigator and others who have access to research records to refuse to disclose identifying information on research subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
- Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.
- By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.
- **For more information, see http://grants1.nih.gov/grants/policy/coc/index.htm.**

39. Is this project principally concerned with the collection of sensitive information such as sexual attitudes, use of drugs or addictive products, and illegal conduct that would need to be protected against subpoena or forced disclosure in order to protect subjects?

☒ No

☐ Yes- will an application for a *Certificate of Confidentiality be submitted to the National Institute of Health upon IRB approval (or approval contingent on the issuance of such a certificate)?

☐ Yes ☐ **No provide a justification as to why a Certificate of Confidentiality will not be obtained:**

40. Describe all procedures that minimize risks, please include study and standard of care procedures:

Skin irritations - Subjects may experience skin irritation from adhesives or tape. Usually this irritation goes away within an hour. The material in contact with the skin can be changed or moved if the subject's skin becomes extremely irritated.

Electrical safety - All devices used in this study incorporate electrical safety components. Cables that are connected to the subject are electrically isolated from the AC-powered

equipment. The entire experimental setup undergoes electrically safety testing every 6 months, or whenever a new piece of equipment is introduced.

Connecting to the BrainGate2 pedestal connector - A strict protocol is followed when making connections to the pedestals. This procedure involves using sterile gloves, antiseptic wipes, and careful alignment and screwing on of the cable connector.

Privacy breach - Identifiable personal information will be kept on VA computers that are encrypted and password-protected. Printed information will be kept at the VA in a locked file cabinet.

41. Describe alternative procedures or course of treatment, if any, which might be advantageous to the subject. State if no alternatives exist or if this is not a treatment study.

This is not a treatment study.

Minimal Risk: Minimal risk means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

42. Please give your overall risk classification for the research:

☐ **Minimal Risk**

☒ **Greater than Minimal Risk**

43. Will subjects receive any <u>direct</u> benefit from this research?

☒ **No** ☐ **Yes** -describe the direct benefits:

44. Please explain briefly why you consider the risks associated with the study to be reasonable in relation to its benefits?

Although the subjects will not receive any direct benefit from this study, they will assist in determining whether a BCI can be used to control multi-dimensional hand and arm movements, which will help optimize future BCI and FES systems that the subjects may receive. The subjects are already participating in the BrainGate2 research study. The risks that are specific to this study are mostly minimal, involving the additional connecting and disconnecting of the BrainGate2 and FES systems.

Section 6 – Informed Consent

45. Type and number of Consent-

- *When more than one consent form is being used a descriptor MUST be in the header section describing the population and/or phase of the study*:

☒ **Written Informed Consent –number used in this study** 1

☐ ***Oral Script/Letter/Information Sheet- number used in this study** ***Submit Request for Consent Waiver Form-waiver of documentation of informed consent**

☐ **No informed consent at all in this study- Submit a Request for Consent Waiver Form-waiver of informed consent and proceed to item 53**

46. Will all adult subjects have the capacity to give informed consent?

☒ **Yes** ☐ **No- Describe range of impairment.**

- *Research involving more than minimal risk, capacity should be determined by a psychiatrist, clinical psychologist, or other qualified professional not otherwise involved in the research.*
- *Individuals who lack the capacity to consent may participate in research only if a legally authorized representative gives consent on their behalf.*

47. Will anyone other than the subject be authorized to provide consent or permission for the subject's involvement in the research?

- *e.g., parents, court ordered guardian, spouse, etc.*

☐ **No** ☒ **Yes** -please explain: Although the subjects will have the capacity to give informed consent, they may not be physically able to sign the consent form, so a legally authorized representative may sign on their behalf.

48. Describe <u>how</u> and <u>where</u> informed consent will be obtained:

Informed consent will be obtained by the investigator's clinical research staff in consultation with the subject. Generally, the process for obtaining informed consent for participation is as follows: 1) a potential subject is referred to the study by a member of the BrainGate study research team. 2) A member of the research staff explains the study. 3) If the subject believes he/she would like to participate in a project, the informed consent and HIPAA authorization forms are presented and reviewed in detail. This occurs in the VA FES Center laboratory. 4) The investigator and/or research staff answer any questions the subject may have, and the informed consent form is signed and dated. If the subject is physically unable to sign the informed consent form, he/she may instruct their legally authorized representative to sign instead. If the subject is physically unable to sign the HIPAA Authorization form, he/she may instruct their legally authorized representative to sign on the Legal Representative line and print their name on the line below. A witness, unrelated to the study personnel, will observe the Legal Representative's signature and will sign elsewhere on the signature page, and write "Witness" next to their signature. This alternate authorization will be documented in CPRS. If the subject does not have a Health Record, the alternate authorization will be documented in the study research file. A de-identified note describing the alternate authorization will also be sent to the IRB. 5) The subject is given a copy of the informed consent and HIPAA Authorization forms to continue to review at his/her leisure.

The investigators inform all prospective subjects about the purpose and experimental nature of the study, the potential hazards and foreseeable risks involved, and the potential benefits that may result from the study. Subjects are informed that they are free to refuse to participate in the study without prejudicing clinical care; and that if they do participate, they will be free to withdraw at any time without prejudicing clinical care. They are instructed to notify the investigators should they decide to withdraw from the study. Patients are not obligated to reveal their reasons for withdrawal or non-participation to the investigator.

49. Will there be an opportunity for potential subject to take the consent form home to discuss participation and options with family members?

☒ **Yes** ☐ **No** - please explain:

50. List by role who will be obtaining informed consent from subjects or their legally authorized representatives:

- *ex. study coordinator, co-investigator, research nurse, research assistant, PI*

Informed consent will be obtained by the PI or study coordinator

51. Please describe how informed consent will be obtained from subjects who do not read or understand English;

- *identify any languages likely to be encountered, and attach a copy of a translated and authenticated informed consent document*
- *It is appropriate to indicate that you do not anticipate encountering potential subjects who do not speak English based on the population to be studied*

For subjects who do not read, the research staff will read the consent form to the subject, and the subject will take the consent form home to allow family and friends to review the form with the subject. Non-English speaking subjects will have already been excluded as a requirement of the BrainGate2 study enrollment, since they will need to understand English instructions during the testing sessions.

52. Describe who *(by Role ex. PI, Coordinator, etc.)* **and how it will be determined that subjects and/or legally authorized representative understand the research and their rights.**

- *ex. question and answer, repeat back parts of the research, describe a procedure...etc*

The investigator or research staff will ask the subject to describe the procedures involved in the study

Section 7 – Privacy and Confidentiality

Privacy - refers to a person's desire to control the access of others to themselves. For example, persons may not want to be seen entering a place that might stigmatize them, such as a pregnancy counseling center that is clearly identified as such by signs on the front of the building. Privacy concerns people, whereas confidentiality concerns data. The research proposal should outline strategies to protect privacy including how the investigator will access information about potential subjects.

In developing strategies for the protection of subjects' privacy, consideration should be given to:

- Methods used to identify and contact potential subjects
- Settings in which an individual will be interacting with an investigator
- Appropriateness of all personnel present for research activities
- Methods used to obtain information about subjects and the nature of the requested information
- Information that is obtained about individuals other than the "target subjects," and whether such individuals meet the regulatory definition of "human subject" (e.g., a subject provides information about a family member for a survey)
- How to access the minimum amount of information necessary to complete the study

Confidentiality - methods used to ensure that information obtained by researchers about their subjects is not improperly divulged. Confidentiality refers to the researcher's agreement with the subject about how the subject's identifiable private information will be handled, managed, and disseminated. The research proposal should outline strategies to maintain confidentiality of identifiable data, including controls on storage, handling, and sharing of data. When appropriate, certificates of confidentiality could be used to maintain the confidentiality of identifiable data

When the IRB evaluates research proposals for strategies for maintaining confidentiality, where appropriate, consideration will be given as to whether:

- Methods to shield subjects' identity adequately protect subject privacy

- There is a long-range plan for protecting the confidentiality of research data, including a schedule for destruction of identifiers associated with the data
- The consent form and other information presented to potential research subjects adequately and clearly describe confidentiality risks.
- The informed consent process and the informed consent document, and if applicable the Authorization Form, clearly delineates who will have access to the subject's information and under what circumstances data may be shared (i.e., government agencies, sponsors).

53. Describe when and where subjects will provide their information. Include the nature of the information and who will receive and use the information. Document the provisions used to protect privacy interests of those subjects when gathering their information and data.

FES Center staff will refer subjects to the study, since we will be recruiting subjects from an existing FES study. We will only get information about a subject if the subject requests that the referrer forwards their contact information to our research team. We would then schedule an appointment for them to sign the HIPAA authorization form and review the consent form. Potential participants will undergo the consenting process in a private room in the VA FES Center laboratory. After the subject signs the consent form, and while still in a private room in the VA FES Center laboratory, the research staff will collect the necessary personal information, such as contact information (name, address, phone number, email address, emergency contact information), demographics information (date of birth, gender, race) and information about their spinal cord injury (injury history, medical status, and medical complications related to the spinal cord injury). This personal information will only be collected at recruitment. The identifiable private information will be kept by the investigator and research staff at the VA. No identifiable private information will leave the VA. The subject will be assigned a research code, and only that code will be used outside the VA to identify the subject. The research code will be used for all other information collected in the study (neural data, stimulation parameters, results of EMG measurements, videos of any procedures performed as part of this study, and written records of incidents related to the study). Even though only de-identified data will leave the VA, due to the small number of subjects (1 or 2 at a time), it is possible that the study sponsor, the local external IRB, and the local research team outside the VA may be able to identify the data. The privacy requirements of the local external IRB will still limit any further identification of the subject data.

54. Will researchers have access to identifiable private information about potential subjects <u>outside</u> of this research project? *Ex. PI is provider who has access to medical records for clinical care*

☒ **No** ☐ **Yes- please explain:**

55. Will Researchers collect identifiable private information on anyone other than the subject?

- *Ex. family members, friends, colleagues, classmates...etc.*

☒ **No** ☐ **Yes -please explain:**

56. At the time data are transcribed or recorded for this study they are?

☐ **Fully identifiable- list identifiers to be collected:**

☒ **Coded with a unique identifier- describe the code:** The code will be 2 letters (representing the study) followed by a 1-2 digit number (representing the subject).

a. Who will have access to the key? The study coordinator and the PI.

b. Where is the key maintained? Two locking barriers must be in place between the coded data and the key. The key will be maintained in a locked cabinet in a locked office in the VA FES Center laboratory (Rm. B-E253), and electronically on a VA server.

☐ **De-identified-by Privacy Officer or Statistician.**

☐ **Other** *(describe)*:

57. How will electronic research data be secured while the study is active?

☐ **No electronic data will be stored**

☐ **VA encrypted laptop**

☐ **Encrypted VA device/media- describe:**

☒ **VA network drive;**

☐ **M: drive; whose?**

☒ **S: drive**

☒ **Folder access password protected**

☐ **Other drive location** *(for example P: drive)*:

☐ **Folder access password protected**

58. How will hardcopy research data be secured while the study is active? Two locking barriers must be in place.

☐ **No hardcopy data will be stored**

☒ **Locked office and locked file cabinet**

☒ **Data coded by PI or study staff with a master list secured and kept separately**

☐ **Data de-identified by Privacy Officer or Statistician-** *(***VA does not consider coded data to be de-identified)**

☐ **Other -specify:**

59. Provide the physical location including room number (and address if outside of this VA) where all electronic and hardcopy data will be stored: Room B-E238 in the VA FES Center laboratories.

60. Is identifiable information physically or electronically sent TO the LSCDVAMC from other institutions or locations?

☒ **No** ☐ **Yes** - contact Privacy Officer Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / 8214101 or Information Security Officer Bruce Frankford bruce.frankford@va.gov / phone 821 1604 – prior to submitting to the Research Service.

****If yes complete the following:**

a. LSCDVAMC investigator will receive:

☐ **Hardcopy information or specimens**

☐ **Electronic information**

b. What are the procedures for transporting and/or transmitting identifiable information securely?

c. What will be the final disposition of the identifiable data transferred to the LSCDVAMC?

- **Record Control Schedule 10-1 indicates that all research records must be retained indefinitely**

61. Is identifiable information physically or electronically sent FROM the LSCDVAMC to other institutions or locations?

☒ **No** ☐ **Yes** contact Privacy Officer Joseph Picklo or Tomica Jefferson joseph.picklo@va.gov / phone 8214102 tomica.jefferson@va.gov / 8214101 or Information Security Officer Bruce Frankford bruce.frankford@va.gov / phone 821 1604 – prior to submitting to the Research Service

****If yes complete the following:**

a. The LSCDVAMC investigator will send:

☐ **Hardcopy information or specimens**

☐ **Electronic information**

b. What are the procedures for transporting and/or transmitting identifiable information securely?

c. What will be the final disposition of the identifiable data transferred offsite?

- **Record Control Schedule 10-1 indicates that all research records must be retained indefinitely**

62. Record Control Schedule 10-1 indicates all research records must be retained indefinitely. Please indicate where this information will be stored and the safe guards to protect it:

a. Electronic Safeguards:

☐ **No electronic data will be stored**

☐ **VA encrypted laptop**

☐ **Encrypted VA device/media- describe:**

☒ **VA network drive;**

☐ **M: drive; whose?**

☒ **S: drive**

☒ **Folder access password protected**

☐ **Other drive location** *(for example P: drive)*:

☐ **Folder access password protected**

b. Hardcopy safeguards. Two locking barriers must be in place.

☐ **No hardcopy data will be stored**

☒ **Locked Office and Locked File Cabinet**

☒ **Coded by Study Staff**

☐ **De-identified by Privacy Officer or Statistician**

☐ **Other- Describe:**

Facility name, address, and room number where hardcopy or electronic data will be stored: LSCVAMC, 10701 East Boulevard, Cleveland, OH 44106. Room B-E238

Section 8 – Data and Safety Monitoring –Greater than Minimal Risk Study

- For all research that is greater than minimal risk a Data and Safety Monitoring Plan must be developed.
- This is a plan to assure the research includes a system of appropriate oversight and monitoring of the conduct of the study to ensure the safety of subjects and the validity and integrity of the data.

***CHECK BOX IF THIS IS A MINIMAL RISK STUDY ☐ SKIP TO #65**

63. Safety monitoring for this greater than minimal risk project will include:

☐ **Data Safety Monitoring Board:**

☐ **Data Monitoring Committee**

☒ **Other**

- *Attach the plan or provide details including whether committee is independent from the study sponsor, how often it meets, whether written reports are available, etc*

We will adhere to the Cleveland FES Center Data and Safety Monitoring Plan Policy. In summary, local IRB approval will be obtained; the PI will monitor adverse events and will provide the required notifications to the IRB and funding agencies; the FES Center Steering Committee will review adverse event trends across projects semi-annually; and annual reports will be provided to the IRB and funding agencies.

64. Describe the plan for on-site data monitoring by the sponsor, contract research organization (CRO), or other independent body: N/A

- **Research Office must be notified of all on-site monitoring visits.*

65. Conditions that may result in removal of subjects from the research *(check all that apply)*:

☐ **Medical condition unchanged**

☐ **Medical condition worsened**

☒ **Serious adverse event**

☒ **Intolerable complications**

☐ **Pregnancy**

☒ **Investigator's clinical judgment**

☒ **Subject withdrawal**

☒ **Subject uncooperative or noncompliant**

☐ **Study closure by sponsor or FDA**

☐ **Refusal to suspend breast-feeding**

☐ **Other-describe:** ☐ **Not Applicable**

66. If a subject withdraws or is removed from the study, describe the potential risks of early withdrawal and the procedures in place to minimize these risks:

This is not a treatment study. There are no risks involved with early withdrawal

Section 9 – FDA-Regulated Drugs/Biologics

NOTE: If this research involves the use of <u>any</u> drugs or biologics, the study is subject to the Food and Drug Administration (FDA) regulations.

- **Documentation of FDA approval for the experimental use of these agents must be provided for review (industry sponsored protocol listing the IND number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IND for this study).**
- All drug/biologic products must be dispensed and tracked through the LSCDVAMC Research Pharmacy.
- An M.D. must be part of the Research Team for all studies that involve the use of a device or drugs.
- The LSCDVAMC Pharmacy and Therapeutics (P&T) Committee must approve: (1) Studies of investigational drugs (2) research involving an FDA-approved drug used in a non-approved manner, and (3) an FDA-approved drug, used as approved, when its use is part of a research protocol.
- **VA Form 10-9012 Investigational Drug Information Record** –must be completed for each drug being evaluated in a research study, regardless of IND status. In addition, the VA Form 10-9012 provides a listing of all authorized prescribers for the study drug(s).

67. Type of Product- check all that apply:

☒ **Not Applicable -No FDA-regulated drugs/biologics involved – Proceed to Section 10**

☐ **Drug**

☐ **Biologic or Other:**

68. Type of Trial *(check as applicable)*:

☐ **Phase I** ☐ **Phase II** ☐ **Phase III** ☐ **Phase IV** ☐ **NA**

Phase I Trials: Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy subjects and/or patients.
Phase II Trials: Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.
Phase III Trials: Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide adequate basis for physician labeling.
Phase IV Trials: Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use.

69. FDA Status of Drugs/Biologics –

*** For drugs, an IND may not be necessary if ALL seven of the following conditions are met:**

1. The drug being used in the research is lawfully marketed in the United States;
2. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
3. The research is not intended to support a significant change in the advertising for the product;
4. The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
5. The research is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively);
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7);
7. The research does not intend to invoke 21 CFR 50.24 (Exception from informed consent requirements for emergency research).

Provide the following information for <u>each</u> drug/biologic used in this study:

Trade and Generic Name	**Manufacturer**	FDA Approved	**Product use consistent with product labeling**	**IND Required***	**IND Number**	**IND Sponsor or Holder****

70. **When the PI holds the IND, complete the following:

i. The PI has reviewed the Guidance on Requirements of the Sponsor and the Investigator as Sponsor

☐ **Yes**

ii. As the PI, you will comply with the regulatory responsibilities of a sponsor

☐ **Yes**

71. Drug Information for each drug listed in the protocol -check as applicable

☐ **Approved Drugs**

☐ **Not Approved**

- **Attach VA Form 10-9012 Investigational Drug Information Record for each drug used in the protocol**
- **Attach Package Insert or PDR monograph – copy ready, 8.5 x 11 for each drug listed in the protocol**
- **Attach Investigator's Brochure**

72. Provide a detailed description of how FDA-regulated drugs/biologics will be stored, secured, dispensed, administered, tracked, and returned.

Section 10 – FDA-Regulated Devices

This section should be completed for a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device.

- An investigational device may be an FDA approved device that is being studied for an unapproved use or efficacy. This also includes an approved device that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.
- Documentation of FDA approval for the experimental use of the device must be provided for review (industry sponsored protocol listing the IDE number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IDE for this study).

Device Risk Determination:

Significant Risk (SR) Device is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject, or (2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non significant Risk (NSR) Device is a device other than a significant risk device.

The IRB is required to document the basis for risk determination based on the proposed use of a device in the research by considering the nature of the harm that may result from the use of the device. FDA has the ultimate decision in determining SR and NSR.

An M.D. must be part of the Research Team for all studies that involve the use of a device.

The Environment of Care Committee (EOC) must approve all research that involves electrically line-operated devices, which have leads or electrodes and will come in contact with human subjects.

73. Type of Product-check all that apply:

☐ **Not Applicable -No FDA-regulated devices involved – Proceed to Section 11)**

☒ **An FDA regulated device will be used BUT not with intent of studying safety or efficacy** (*Proceed to Section 11)*

☐ **Device**

74. List the device-include name and manufacturer:

75. FDA Regulatory Status of the Device:

☐ **FDA Approved Device**

- **A device approved by the FDA for distribution, marketing, sale to, and use by, the public for the study's indication.**

☐ **New Indication of an FDA Approved Device**

- **A device NOT approved by the FDA for distribution, marketing, sale to, and use by, the public for the indication used in the study.**

☐ **Investigational - Investigational Device Exemption (IDE)**

- **An FDA designation that permits a manufacturer to lawfully ship an unapproved device for use in a research study.**

Provide the following:

a. **IDE Number:**

b. **IDE Sponsor or Holder:**

If the PI holds the IDE, complete the following:

i. **The PI reviewed the Guidance on Requirements of the Sponsor and the Investigator as Sponsor**

☐ **Yes**

ii. **As the PI, you will comply with the regulatory responsibilities of a sponsor**

☐ **Yes**

c. **FDA or Sponsor Device Risk Determination**

☐ **Non-Significant Risk**

☐ **Significant Risk**

d. **Attach documentation of FDA approval for the experimental use of the device (industry sponsored protocol listing the IDE number, letter from the FDA, letter from industry sponsor, or other document and/or communication verifying the IDE for this study).**

☐ **Humanitarian Use Device (HUD)**

- **An FDA designation for a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. For more information about Humanitarian Use Devices see the HRPP SOP manual on the R&D website.**

Provide the following:

a. **HUD Number:**

b. **HUD Sponsor or Holder:**

c. **Include a copy of the FDA letter granting Humanitarian Use Device (HUD) status.**

☐ **510(k) Status –**

- **A device determined by the FDA to be "substantially equivalent" to an existing device that is legally marketed in the U.S. Until a 510(k) device is approved, it is still considered investigational.**

a. **Provide the name of an equivalent device and sufficient documentation to justify 510(k)**

76. Attach device information (i.e., brochure, device label)

77. Provide a detailed description of how FDA-regulated devices will be stored, secured, dispensed, administered, tracked, and returned.

Section 11 – Genetic Testing and Discovery of Genetic Information (DNA)

78. Does the research involve genetic testing or DNA/RNA extraction?

☒ **No genetic testing** (*Proceed to Section 12)*

☐ **Yes- complete the following:**

a. Describe the purpose of the genetic testing component of the study

- *Is it to establish risks, associations, or prevalence?*

b. Describe whether the test is a standard test already in clinical use or a new or experimental laboratory study

c. Describe the accuracy of the test

- *Sensitivity, specificity, reliability, validity, and variability*

79. Does an abnormal test result indicate that the subject:

☐ **Has a specific condition**

☐ **Is at risk for a specific condition**

☐ **May be at risk for a specific condition**

☐ **Has, is, or may be at risk for some other outcome**

☐ **Other** *(describe):*

80. Does a normal test result indicate that the subject

☐ **Is not at risk for a specific condition**

☐ **Is at a lower risk for a specific condition**

☐ **Is at a population risk for a specific condition**

81. Is there a risk of discovery of other results such as non-parentage or other genetic conditions?

☐ **No** ☐ **Yes- please explain:**

82. Will test results produce information on anyone (e.g. a first-degree relative) besides the subject?

☐ **No** ☐ **Yes- please explain:**

83. To whom and in what manner will genetic information be reported?

84. Will genetic counseling be made available to subjects?

☐ **No** ☐ **Yes- indicate who will conduct the counseling and whether there are any additional charges:**

85. Will DNA samples be stored?

☐ No ☐ Yes--describe where, how, and for how long the samples will be stored:

86. Who will own the DNA samples?

87. Will there be any subsequent analysis of the DNA samples?

☐ No ☐ Yes- describe the purpose of the subsequent analysis and whether there will be dissemination of any new information:

88. Describe how samples will be handled if the subject withdraws consent for further participation:

89. Will the samples be distributed to other investigators?

☐ No ☐ Yes- please explain:

90. Describe the provisions to maintain the confidentiality of research data, especially in cases where data can be linked to individual subjects:

Section 12 – Tissue Collection/Storage/Banking*

It is VA policy to ensure that human biological specimens, as well as the linked data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations, are maintained at *VA approved tissue banks or VA-sponsored tissue banks.

See VHA Directive 2000-043 "Banking of Human Research Subjects' Specimens" for more information and also visit http://www.research.va.gov/programs/tissue_banking/default.cfm

Human biological specimens (specimens).

- **Human biological specimens are materials, such as blood, urine, tissue, organs, hair, nail clippings, buccal swabs or any other materials that are derived from human subjects and are either collected specifically for research purposes or as residual specimens from diagnostic, therapeutic or surgical procedures.**

91. *Does the research involve storage or banking of human specimens or identifiable private information for use in future studies? *(check all that apply)*

☒ **No** *(proceed to Section 13)* ☐ **Yes-describe status of VA approved or VA sponsored facility:**

☐ **Storing or banking identifiable private information**

☐ **Storing or banking human specimens**

Please provide the following information:

a. What identifying information will be required?

b. What are the foreseeable uses of the specimens (e.g., research, pharmaceutical products, production of cellular lines for various uses, etc.)?

c. What is the VA approved or VA sponsored location/institution where the information and/or specimens will be stored?

d. How long will the information and/or specimens be stored?

e. Is the storage facility an on-site or off-site location?

f. Will subjects be able to request that their specimen and/or information be withdrawn from the bank or repository? *(explain)*

Section 13 – Children as Research Subjects

Research involving children must not be conducted by VA investigators while on official duty or at VA or VA-approved offsite facilities unless a waiver has been granted by the CRADO (See VHA Directive 2001-028 "Research Involving Children" for more information.

92. Do you plan to enroll children as research subjects?

☒ **No** *(Proceed to Section 14)*

☐ **Yes- Age range of subjects:**

93. Category of Research *(Check the box next to the category of research you believe your research falls under. The IRB will make a final category determination during review.)*:

☐ **Research involving minimal risk (the probability & magnitude of harm or discomfort anticipated are not greater than those ordinarily encountered in daily life or during routine physical or psychological tests.)** *(46.404)*

☐ **Research involving greater than minimal risk but of potentially direct benefit to the subject.** *(46.405)*

☐ **Research involving greater than minimal risk and no prospect of direct benefit to the subject but likely to yield generalizable knowledge about the subject's disorder or condition.** *(46.406)*

☐ **Research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting children/decisionally impaired adults.** *(46.407)*

94. Do you anticipate enrolling minors who are wards of the state?

☐ **No** ☐ **Yes**

95. Permission of parents or guardian *(check one only)*:

☐ **The permission of each child's parents or guardian will be sought unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child (required for categories 46.406 and 46.407 above in item 104).**

☐ **The permission of only one parent will be sought (acceptable for categories 46.404 or 46.405). If marked, provide justification:**

96. Assent of Children *(check one only)*:

☐ **The assent of each child who is capable of providing assent based on age, maturity, and psychological state will be sought.**

☐ **The assent of each child will not be sought because the capability of all of the children in this study population is so limited that they cannot reasonably be consulted. Explain why the capacity is so limited, e.g., age, maturity and/or psychological state:**

☐ **The assent of each child will not be sought because the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research. Explain what the direct benefit may be and why it is only available in the context of the research:**

Section 14 – Other

97. Please describe any other study procedures not referenced in the previous sections:

☒ **Not applicable**