Study Protocol and Statistical Analysis Plan

Official Title: Targeted HD-tDCS for Reducing Post-stroke Movement Impairments

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Principal Investigator: Yuan Yang, Ph.D., Stephenson School of Biomedical Engineering, University of Oklahoma

Co-Principal Investigator: Evgeny Sidorov, M.D., Ph.D., Department of Neurology, University of Oklahoma Health Sciences Center.

Project Biostatistician Co-investigator: Shirley James, PhD, PT, Hudson College of Public Health, Department of Biostatistics and Epidemiology, University of Oklahoma Health Sciences Center.

Abstract
Stroke is the leading cause of serious, long-term disability. The emergence of abnormal muscle synergies following a stroke presents a major limitation to the recovery of independent function. Despite the development of many interventions for movement recovery post-stroke, rehabilitation treatments are minimally effective to muscle synergy impairment. Treatment advances have been hampered by our poor understanding of neural plasticity post-stroke and the overall lack of precise interventions in neurorehabilitation. Thus, our long-term objectives are to 1) improve the understanding of the underlying neurobiological mechanism of neural plasticity that drives the recovery of motor function; 2) develop targeted interventions that improve stroke rehabilitation in more impaired individuals. Our previous studies have found that muscle synergy impairment is associated with the damage to the corticospinal tract and the maladaptive recruitment of contralesional cortico-reticulospinal tract. We hypothesize that facilitating the damaged cortico-spinal tract (via primary motor cortex) and/or inhibiting the contralesional cortico-reticulospinal tract (via dorsal premotor cortex) will reduce muscle synergy impairment and improve upper extremity motor function. In this OSCTR pilot project, we propose to run a proof-of-concept pilot trial to evaluate the effect of the targeted high-definition transcranial direct current stimulation (HD-tDCS) on mitigating the muscle synergy impairment. This study will determine the effect of the proposed targeted HD-tDCS on reducing the upper limb motor impairment, via a pilot trial with a randomized, double-blinded, sham-controlled cross-over design.

A. Specific Aims

Stroke is the leading cause of serious, long-term disability. Three months after a stroke, 80% of individuals with moderate to severe stroke report movement impairment on the side of the body contralateral to the lesioned hemisphere[1]. The specific movement impairments include a loss of fine motor control with the emergence of highly stereotyped patterns of coarse, multi-joint movements, clinically known as muscle synergies[1]. Despite the development of many interventions for movement recovery post-stroke, rehabilitation treatments are minimally effective to the muscle synergy impairment in more impaired individuals. Treatment advances have been hampered by our poor understanding of neural plasticity post-stroke and the overall lack of lack of precise intervention in neurorehabilitation. Thus, our long-term objectives are to 1) improve the understanding of the underlying neurobiological mechanism of neural plasticity that drives the recovery of motor function; 2) develop targeted interventions that improve stroke rehabilitation in more impaired individuals.

As a result of damage to the corticospinal tract in the lesioned hemisphere, there is evidence of upregulation of cortico-reticulospinal tract excitability in the contralesional side (i.e., the opposite side to the lesion)[2]. Both animal and human studies (including the PI Yang's multi-sites R21 study[3-5]) in stroke suggest and support the critical role of maladaptive use of the contralesional cortico-reticulospinal tract to post-stroke movement impairments,[2, 6] specifically, the presence of spasticity exhibited by upper extremity muscle synergies[3-5]. Previous studies applying *transcranial magnetic stimulation* (TMS) to patients after stroke demonstrated that the use of the contralesional cortico-reticulospinal tract requires cortical input from the premotor cortex at the non-lesioned hemisphere[7, 8]. These studies provide potential targets of facilitating the damaged corticospinal tract (via the primary motor cortex) and/or inhibiting the contralesional cortico-reticulospinal tract (via the premotor cortex) for intervention.

In this project, we propose to run a proof-of-concept trial to evaluate the effect of the targeted HD-tDCS on mitigating the motor impairment, via the following two specific aims.

Aim 1. Demonstrate the feasibility of stroke subject recruitment and retainment. Our pilot power analysis determined that at least 40 stroke patients will be needed in a full R01 trial. We **hypothesize** that our experimental site at the OUHSC campus has the full ability to recruit 12 eligible patients in one year and retain most of them to complete this trial (detailed in Aim 2).

Aim 2. Determine the effect of the targeted HD-tDCS on reducing the upper limb motor impairment. We **hypothesize** that: 1) facilitating the ipsilesional primary motor cortex will improve the function of the damaged corticospinal tract and therefore, reduce upper limb muscle synergies. 2) inhibiting the contralesional premotor cortex will reduce the maladaptive use of the cortico-reticulospinal tract and thus, also reduce impairment. This randomized, double-blinded, sham-controlled cross-over study will include the anodal HD-tDCS targeting the **ipsilesional primary motor cortex (Aim 2a)**, and the cathodal HD-tDCS over the **contralesional premotor cortex (Aim 2b)**, compared to sham stimulation. We will use a subset of Fugl-Meyer Upper Extremity assessment which is mainly related to the muscle synergies[9] as the primary outcome measure. The TMS-induced motor-evoked potentials (MEP) will be measured to determine the use of ipsilesional corticospinal tract and the contralesional cortico-reticulospinal tract[7, 8], with the MEP latency as the secondary outcome measure[7, 10]. Resting-state EEG will also be obtained to have the *brain symmetry index*[11] as the third outcome measure for evaluating the acute effort of HD-tDCS on brain plasticity.

B. Background and Significance

Stroke survivors account for 795,000 adults per year and approximately 7 million individuals living in the US (data from CDC and AHA websites). In stroke rehabilitation research, individuals exhibiting moderate-to-severe upper limb impairment after stroke are underserved and under-investigated. Reviews of existing studies indicate that treatments are minimally in improving of upper limb function(12). Moreover, constraint-induced therapy, a well-established clinical technique, requires a large dosage (30-40 hours/week) that is not always feasible in the current healthcare climate nor can it be used in individuals with more severe motor impairment(12). New interventions are needed that can easily translate to the clinic. Improved intervention strongly relies on our understanding of neural circuitry changes in the motor system after a stroke and how they could be positively and specifically influenced by neuro-rehabilitation technology. Previous studies (including the PI's R21 study(3-5)) found that post-stroke muscle synergy impairment is associated with increased recruitment of the contralesional cortico-reticulospinal tract, following damage to the corticospinal tract at the lesioned side(2, 6) (Fig.1). This finding provides potential neuro-targets to reduce muscle synergies, i.e., facilitating the use of the lesioned corticospinal tract or inhibiting the recruitment of the contralesional cortico-reticulospinal tract. This pilot study will provide the first preliminary data to evaluate the effect of our novel targeted HD-tDCS intervention on reducing upper limb muscle synergies. **This proposal is significant because it targets patients who have had strokes and continue to experience muscle synergy impairment with limited options for improving upper limb movement.**

C. Preliminary Studies/Progress Report

The contact PI Yang has collected pilot data from both his previous institute Northwestern Medicine, as well as in his current Tulsa lab (OU #IRB 12550). The data demonstrated the feasibility of proposed HD-tDCS technology, showing both anodal (over the ipsilesional primary motor cortex) and cathodal (over the contralesional premotor cortex) HD-tDCS reduced the expression of muscle synergies (Fig. 2). The anodal HD-tDCS reduced the latency of MEP of the damaged corticospinal tract while the cathodal HD-tDCS increase the latency of the MEP of the contralesional cortico-reticulospinal tract. Thus, the previous pilot data support our hypotheses that 1) facilitating the ipsilesional primary motor cortex will improve the function of the damaged corticospinal tract and enhance upper limb movement. 2) inhibiting the contralesional premotor cortex will reduce the maladaptive use of the cortico-reticulospinal tract and reduces the synergy impairment.

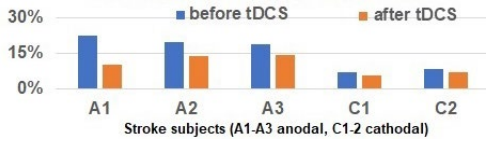

Fig. 1. Reduced expression of muscle synergies after the targeted HD-tDCS. A1-3 Anodal, C1-2 Cathodal.

D. Research Design and Methods (What, When, How, Where)

The statistical analysis of our preliminary data indicated that 40 stroke participants are required to ensure the detection of the significance of our results in a complete trial. We will screen up to 50 patients to ensure we can enroll at least **12 stroke** participants in the first year as the pilot sponsored by OSCTR pilot grant. The participants living around the Oklahoma City area (main site) will be asked to come to:

- OU Physician Neurology Clinic 825 NE 10th Street ,Oklahoma City, OK 73104 (the primary site).
- College of Allied Health at the University of Oklahoma Health Sciences Center located at 1200 N. Stonewall, Oklahoma City, OK 73117 (the secondary site)

Baseline standard clinical screens including the Fugl-Meyer Motor Assessment (Upper Extremity Portion) will be conducted prior to any intervention trials.

Overall Overview of Trial Design. This **sham-controlled cross-over study design** will include three visits: 1) anodal stimulation targeting ipsilesional hemisphere, 2) cathodal stimulation at the contralesional hemisphere, 3) sham stimulation. The sequence of the stimulations will be **randomized and double-blinded**. After each intervention, there will be a 2-week **wash-out period** (minimum) prior to providing the next intervention in the sequence. Each visit will last up to 3 hours including the preparation time and breaks.

We will use neuro-navigation high-definition tDCS (NNG HD-tDCS) to target specific brain regions in a novel and precise manner. A subject-specific head model will be built to evaluate the effect of lesion size and location on the electrical field of tDCS. The MR images (or CT images) will be used to build these subject-specific head models. The stimulation electrode montage and inter-electrode distance will be carefully examined by computer simulation to determine the optimal setup and dosage for NNG HD-tDCS. Based on our pilot test, the stimulation dosage will be set as 2 mA, 20 min, the dosage for best-influencing neuroplasticity according to the safety guidelines of HD-tDCS(13,14).

Assessments and Outcome Measures. The following assessments will be performed for baseline, pre- and (immediate) post-intervention time frames. The Fugl-Meyer-Upper Extremity (FM-UE) assessment Part A - mainly related to the muscle synergies[9] and serves as the primary outcome measure. This subset FM-UE assessment increases the sensitivity of the measure and reduces the test time from 30 mins (full assessment) to 10 mins[9]. The TMS-evoke motor-evoked potentials (MEP) will be measured to determine the use of the ipsilesional corticospinal and the contralesional cortico-reticulospinal tract[7, 8], with MEP latency serving as the secondary outcome measure[7, 10]. The single or paired-pulse TMS will be applied at the respective hotspots for the elbow flexor muscle, i.e., Biceps Brachii, over the ipsilesional primary motor cortex (from which the corticospinal tract originates) and contralesional premotor cortex (from which the cortico-reticulospinal tract originates) with reference to the impaired arm[13, 14]. A 3 min 20 channel Resting-state EEG will also compute the *brain symmetry index* (BSI)[11] as the third outcome measure for evaluating the acute effort of HD-tDCS on brain plasticity. The BSI is defined as the mean of the absolute value of the difference in the mean hemispheric amplitude spectrum; values range from 0 (no asymmetry, normal control) to 1 (maximal asymmetry, more impaired brain function)[11]. The total three assessments will last for ~33 min (10 mins subset FU-UE assessment, ~10 mins TMS MEP, and 3 mins EEG recording plus 10 mins procdure time), which will be within the effective period of HD-tDCS[15]. Baseline measurement will be performed at the beginning of the study on the first visit. To ensure there is no carry-over effect, we will compare the outcomes of pre-stimulation measurement with the baseline for each visit.

All recorded data will be de-identified for the analysis. Identifiers might be removed, and the de-identified information may be used for future research without additional informed consent from the subject.

E. Chart Review

Chart review (including available medical records and MRI/CT) and enrollment will be performed by our study doctor Co-PI Dr. Sidorov.

F. Banking/Repository/Database

The recorded data (EEG, MEP and clinical assessments) will be de-identified and stored for future use. These data may be used as preliminary data for a future large R01 grant application. These data may be re-analyzed for data science projects or publications.

The data will be in OU/OUHSC using the Shared Services File Storage Service offered by OU/OUHSC IT. Shared Services File Storage service offers a secure, state-of-the-art clustered storage system for the research team's data and files, similar to typical Windows or Linux file shares. This service features a robust filesystem utilizing high-speed networking for faster access and enables the research team to store and access files from on or off-campus (with VPN) using Windows, Mac OSX, or Unix/Linux operating systems in a secured way.

G. Inclusion / Exclusion Criteria

Stroke participants should have sustained an ischemic unilateral lesion (confirmed by the most recent clinical or radiological reports) at least 3 months prior to participation in this project. The following inclusion criteria will be applied to the stroke participants: 1) Paresis confined to one side, with moderate to severe motor impairment of the upper limb (Fugl-Meyer upper extremity scores of 10-40); 2) Absence of muscle tone abnormalities and motor or sensory impairment in the unimpaired limb; 3) Absence of severe wasting or contracture or significant sensory deficits in the paretic upper limb; 4) Absence of severe cognitive or affective dysfunction that prevents normal communication and understanding of consent or instruction; 5) Absence of severe concurrent medical problems (e.g. cardiorespiratory impairment); 6) Capacity to provide informed consent; 7) Not using a pacemaker, 8) No metal implants in the head 9) No known adverse reaction to TMS and tDCS; 10) Capacity to provide informed consent; 11) Not pregnant.

We are not performing specific assessments since the main goal of our study is to investigate the motor function and movement recovery after stroke. If participants can communicate with the researcher, and understand the procedures well and have the ability to consent, they meet this criterion (5). Stroke participants using a wheelchair or other assistive mobility devices are eligible to participate if they meet the inclusion criteria (1)-(11).

There may be circumstances under which participation may be terminated by the investigator without consent. The examples may include but not limited to:

- The investigator feels that it is in the individual's best interest.
- The individual's condition worsens, or any new condition makes the individual no longer qualified for this study.
- New information becomes available resulting in the individual no longer meeting the inclusion criteria.
- The individual fails to follow study requirements.
- The study is stopped by the sponsor.

H. Gender/Minority/Pediatric Inclusion for Research

Women and minorities eligible to participate in our study based on our inclusion criteria will be actively recruited to mimic the gender and race/ethnicity distribution in stroke survivors. The most recent update on Heart Disease and Stroke Statistics from the American Heart Association includes data on the prevalence and incidence of stroke among women and minorities. Both of these statistics vary by age and race/ethnicity but on average indicate a similar prevalence between males and females (2.4 vs 2.9% of Americans ≥ 18 y) with similar prevalence within race/ethnicity of non-Hispanic white, black, and Hispanic males and females (2.2 vs 2.8%, 3.9 vs. 4.0% and 2.0 vs 2.6% of Americans ≥ 18 y). The incidence of new and recurring attacks across all ages is slightly higher in females compared to males (53.5 vs 46.5% of Americans ≥ 18 y). Annual age-adjusted incidence for the first-ever stroke was higher in black individuals than white individuals in data collected from 1993 to 1994, 1999, and 2005 and reflected in the prevalence statistics. In addition, the age-adjusted incidence of first ischemic stroke per 1000 was 0.88 in whites, 1.91 in blacks, and 1.49 in Hispanics according to data from NINDS for 1993 to 1997. Finally, a smaller study in Texas found a higher incidence of ischemic stroke among Mexican-

Americans compared to non-Hispanic white Americans.

Although there is no theoretical basis upon which to assume that gender or race/ethnicity differences will affect movement control following brain injury in the upper limb, we will nonetheless use our quantitative measure of maximum reaching abduction load to evaluate gender and race/ethnicity differences in abnormal joint torque coupling.

The risk of pediatric stroke is approximately 5 per 100,000 children. Our laboratory environment has been designed such that children age 6 and up can have access to our experimental facility. However, the impact of age/development of the nervous system and the timing of brain injury in children is still unclear, which could be very different from the adult stroke. This study focuses on the exploration of our innovations in studying adult stroke survivors, and, therefore, children will not be recruited for the study.

I. Recruitment and Enrollment

Our primary patient resource is from OU Physician Neurology Clinic and Allied Health Clinical Network. We will also seek referrals from clinicians in the Oklahoma City areas and recruit stroke survivors residing in these two areas who wish to participate in the study. The recruitment method will include doctor referrals and direct contact (if study doctor's patients) via the study doctor.

Stroke participants will be examined by the study doctor to verify their admissibility to the study based on the inclusion criteria. Participants will then undergo the upper extremity portion of the Fugl-Meyer Motor Assessment, and a structured interview pertaining to the inclusion criteria stated above.

Our clinician investigators and/or clinical research assistant will discuss the proposed study with potential participants and answer all questions. Potential participants will also be introduced to laboratory facilities at study sites. The PI will review the Institutional Review Board-approved consent form and HIPAA authorization with the participant and give them a copy of the signed consent form prior to any experimental procedures. Upon the request, we will allow the participant to have additional time to consider the consent and discuss it with their family member or physician. The participant must sign both the consent form, as well as the HIPAA form prior to participating in this study.

J. Risks and Benefits

The self-adhesive surface electrodes used to record muscle activity (EMG) may produce minor irritation of the skin; there is also the possibility of an allergic reaction to the electrode paste. The possibility of irritation will be minimized by cleaning the skin with alcohol before and after the application of the electrodes. There is a similar possibility of scalp irritation due to a reaction to the use of EEG/tDCS electrodes.

The tDCS may cause transient itching and tingling at the beginning of the delivery of stimulation due to the change of voltage/current as it ramps up to the targeted intensity. However, most people reported that these are very mild and fade quickly. A small number of participants may report moderate fatigue, particularly during, but not after stimulation. Minor scalp skin irritation may occur but will be minimized by screening participants who self-report having sensitive skin (based on the tDCS Safety Screening Tool (TSST)(16)).

If stroke patients participate in this study, possible benefits may include an improved ability to control their paretic arm during movement tasks. Benefits may or may not continue after the research has ended. Possible benefits to others include an enhanced understanding and treatment of movement disturbances following a stroke.

K. Multiple Sites

Dr. Yang will be the lead PI and Dr. Sidorov will be Co-PI and study doctor for the whole study. The study includes three visits at one of the following sites:

- OU Physician Neurology Clinic 825 NE 10th Street Oklahoma City, OK 73104 (the primary site).

- College of Allied Health at the University of Oklahoma Health Sciences Center located at 1200 N. Stonewall, Oklahoma City, OK 73117(backup site)

Dr. Yang and Dr. Sidorov (the chief study doctor) will oversee the study and will be responsible to report adverse events occurring in the Oklahoma City site to the OUHSC IRB office.

L. Statistical Analysis Plan

The statistical and power analysis will be led by Dr. Shirley James, Assistant Professor of Research in Department of Biostatistics & Epidemiology, Hudson College of Public Health within the University of Oklahoma Health Sciences Center. The obtained preliminary data will refine our power analysis to provide a more precise estimation of sample size for a future full trial. The effect of HD-tDCS is determined by the change in Fugl-Meyer upper extremity Part A score (primary outcome measure), change in Transcranial Magnetic Stimulation (TMS)-Evoke Motor-evoked Potentials (MEP, secondary outcome measures), and change in Brain Symmetry Index (other outcome measures). All statistical analysis was completed using commercial software Statistical Analysis Systems (9.4, SAS, Carey, NC, USA). After checking for and finding no evidence of a non-normal outcome measure distribution, we analyzed the data using generalized estimating equation (GEE) in SAS using PROC GENMOD. The fixed factors are group (anodal, cathodal, sham), time (pre and post intervention), and their interaction, and the random factor is subject ID. This technique uses correlated linear models for each outcome variable (17,18).

M. Data and Safety Monitoring Plan

Overall framework for safety monitoring and what information will be monitored.

The PIs will be responsible for ensuring participants' safety on a daily basis due to the low risk of this mechanistic clinical trial study. All reportable new information (safety data) will be reported to the IRB within 5 days per University policy by the PI following a review with the study team and DSMB. These include but are not limited to new or increased risks, adverse events, serious adverse events, non-compliance with IRB policy, researcher error/protocol violation, and unresolved participant complaints.

Research data will be monitored for completeness every week. The RedCap™ (Research Data Capture) system will be utilized to store all patient demographic information (coded), clinical assessment scores, and all processed data via encrypted university computers. The raw/unprocessed data be coded with a unique patient identifier and stored offline on an encrypted and password protected laboratory computer and backed up to secure online storage through the Shared Services File Storage Service managed by OU/OUHSC IT. Raw data on the computer cluster will be accessible only to study investigators.

Frequency of monitoring plans for interim analysis and stopping rules.

A monthly summary of reportable new information (safety data) will be made by the Clinical Research Coordinator (covered by the subcontract to OUHSC), in collaboration with team members in the project and then reviewed by the PIs. Raw research data will be reviewed weekly by the study investigators for organization, completeness, and confirmation of backup. Data quality issues, if any, will be discussed with the investigators and recommendations will be made for immediate solutions by the investigators. An interim analysis will be conducted on research data and directly available to the Program Officer on request. Due to the low risk of the proposed study, minimal adverse events are expected, and no 'a priori' stopping rules will be assigned.

Management and reporting of adverse events and serious adverse events.
Upon first knowledge of an adverse event or serious adverse event (also including any reportable new information), the event will be reported to the clinical research coordinator. After reviewing with the PIs, the OUHSC clinical research team, and relevant personnel, the clinical research coordinator will generate the IRB report and queue for review and submission by the PI to the IRB within 5 days per University/IRB policy. A copy will also be sent to the Office of HRPP. The study PI will report all adverse and serious adverse events to the NIH within the same time frame. The PI will have weekly meetings with team members to review all reportable new information.

Individual responsible for study monitoring
Overall study monitoring will be the responsibility of the study doctor and PI. The study doctor and PI will utilize a clinical research coordinator to prepare safety and data monitoring reports as required.

N. Data Sharing

We are committed to enhancing the value of research and furthering the advancement of public knowledge. We recognize that the public dissemination of our scientific results can facilitate the creation of collaborative efforts with domestic and international collaborators. Furthermore, we recognize that the proposed project may result in novel ideas for new methods, technologies, and data that could benefit the entire research community. Therefore, final research data will be shared openly and timely in accordance with the most recent NIH guidelines (http://grants.nih.gov/grants/policy/data_sharing/) while being mindful that the confidentiality and privacy of participants in research must be protected at all times.

More specifically, sharing of data and resources generated by this project is an essential part of our proposed activities and will be carried out in several different ways including presentations at national scientific meetings, and publications in peer-reviewed journals. We wish to make our results available to the community of scientists interested in stroke rehabilitation and to help avoid unintentional duplication of research. All research data obtained at this study will be shared with members in our interdisciplinary team across the University of Oklahoma (OU) and OU Health Sciences Center (OUHSC). We welcome collaboration with others (outside our team) who can fruitfully use and apply the rehabilitation plan we developed in this pilot trial and following R01 study. The research team shall create and maintain a database to integrate de-identified clinical assessment results and acquired EEG, EMG, behavior data, in order to facilitate data sharing. The database shall be accessed through a secured web portal. All investigators at this project will employ best practice implementations for accessing the data via institute-owned, encrypted computers to increase the security of the network and to assure the availability, integrity, and confidentiality of information. Any data distributed to additional potential research collaborators outside of this project will be de-identified prior to sharing to preserve the confidentiality of the participants' identity to protect Human Subject Privacy.

The results of this pilot trial will be disseminated through ClinicalTrials.gov, in accordance with institutional policies that ensure compliance with NIH policies on clinical trial registration and reporting. The results of the study will also be disseminated through publications and presentations at national/international meetings, and discussed at local seminars. The PI Dr. Yang together with clinician investigator Co-PI Dr. Sidorov will be responsible for handling ClinicalTrials.gov requirements for this project. The trial will be registered with ClinicalTrials.gov prior to enrolling in the first subject. Once a record is established, Dr. Yang and Dr. Sidorov will confirm the accuracy of record content; resolve problems; maintain records including content updates and modifications; and aggregate results reporting at the conclusion of the project and adverse event reporting (if any). All reporting and submission of results will occur within the timeframes in the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. Informed consent documents for this clinical trial will include a specific statement relating to the posting of this trial's information and results at ClinicalTrials.gov.

We will make available final research data when findings from our study are accepted for publication, as recommended in NIH guidelines on data sharing. While there will be no restrictions on access, the distribution of final research data will be strictly controlled and documented based on university policies and the NIH Principles and Guidelines document. Data requests will require registration, including a valid email address. The PI will issue (by email) to each requestor a password that will allow access to a cloud-based download page, and data will be downloaded over an encrypted (SSL2) connection. We will make all analysis tools, algorithms, software interfaces, source codes and documentation, modeling tools, and other software technologies developed and/or enhanced during the project freely available to the scientific community with an open-source license through the lab website. If any source code is developed in the course of analyzing the data collected in the study, we will also deposit source code in open-source libraries. Should any intellectual property arise which requires a patent, we will ensure that the technology (materials and data) remains widely available to the research community in accordance with university policies and the NIH Principles and Guidelines document. In general, we expect the data will be available through speaking engagements and publications, presentations at scientific symposia and seminars. The effort will be made to publish our research findings in scientific journals.

All published work will likely be presented in abstract form at relevant international conferences of the American Society of Neurorehabilitation, Society for Neuroscience, American Heart/Stroke Association, American Physical Therapy Association, American Congress of Rehabilitation Medicine, etc.

O. Confidentiality

OUHSC RedCap™ (Research Data Capture) system will be utilized for the storage of all patient demographic information (coded), clinical assessment scores, and all processed data via encrypted university computers. The raw/unprocessed data be coded with a unique patient identifier and stored offline on an encrypted and password protected laboratory computer and backed up to secure online storage through the Shared Services File Storage Service managed by OU/OUHSC. Raw data on the computer cluster will be accessible only to study investigators.

All recorded experimental data (including videos) will de-identified before the analysis. The database shall be accessed through a secure web portal. All investigators employ best practice implementations for personal computers to increase the security of the network and to assure the availability, integrity, and confidentiality of information. Any data distributed to additional potential research collaborators outside of the study team will be de-identified prior to sharing to preserve the confidentiality of the participants' identity.

With written permission from the subjects, video recordings may be performed using a regular camera. The videos will be used to detect the abnormal movement patterns from the stroke subjects to aid with data analysis. All videos will be de-identified by adding a face cover to the subject's image. However, it may not be destroyed after the study since the result from video analysis may be a part of our publications. The videos as the original data will be saved in an encrypted and password protected laboratory computer and backed up to secure online storage through the Shared Services File Storage Service managed by OU /OUHSC IT.

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