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1. INTRODUCTION

1.1 General overview

Spinal cord injury (SCI), a common cause of devastating paralysis, carries some sobering statistics: SCI affects nearly a million people in the U.S. alone. Of these, some 150,000 are U.S. veterans, according to the Christopher & Dana Reeve Foundation. Almost 12,000 new cases are added each year, following road-vehicle and military service-related injuries. SCI patients often lose feeling and movement in the upper body and all four limbs. They must then depend on family members and caregivers to meet every personal need, from feeding, bathing/toileting, and dressing to participating in family and community activities. SCIs mostly occur in adults between the ages of 28 and 43, in what would normally be their most productive years. The lifetime costs of managing such a disability are staggering: about $4.7 million per patient. In this project, three healthcare centers will test a new nonsurgical approach to help SCI patients (veterans and civilians) more quickly regain some of their lost functions.

1.2 Purpose

Primarily, the purpose of this phase I/II clinical trial for patients living with cervical spinal cord injury (SCI) is to promote recovery of the paretic upper limb and improve functional independence by using non-invasive brain stimulation (tDCS) in combination with upper limb rehabilitation to recruit any and all residual spared neural resources.

Secondarily, the clinical trial will determine the safety and feasibility of pairing tDCS with rehabilitation in individuals with SCI.

1.3 Duration of the Investigation

The estimated duration of this clinical trial is 5 years from the time of first subject enrollment to the last follow-up visit for all patients enrolled.

1.4 Site Information

Cleveland Clinic will serve as the lead site for the study. Dr. Ela Plow will be the lead PI and Mr. Kyle O'Laughlin will be the lead coordinator. Each of the four sites will have a clinical coordinator (Mr. O' Laughlin at the Cleveland Clinic, Ms. McCabe at the Cleveland VA Medical Center, Ms. Friedl at MetroHealth Hospital and Ms. Martinez at Kessler Foundation/Kessler Institute for Rehabilitation). Mr. O' Laughlin with supervision from Dr. Plow will help establish, maintain and monitor compliance with Good Clinical Practices (GCP) and Good Laboratory Practices (GLP).

To ensure standardization of methodologies across all sites (Cleveland Clinic Foundation, Cleveland VA Medical Center, MetroHealth Hospital, and Kessler Foundation/Kessler Institute for Rehabilitation), and proper recording of data, we will adopt the following safeguards:

- *Functional Outcome Measures*
  For this multi-site study two study staff from the Cleveland Clinic (Dr. Plow and Mr. Kyle O'Laughlin) will travel to the Cleveland VA Medical Center and Kessler Foundation/Kessler Institute for Rehabilitation to educate other site study staff in functional outcome methodology. At this time, any alterations as suggested by Dr. Kirshblum and Dr. Richmond (SCI physicians from Kessler Rehab Institute and Cleveland VA respectively) and Anne Bryden (OTL/R from Metrohealth Hospital) will be implemented. We anticipate

that this will occur by November-December 2018 (~3 months into the study). Should any alterations in functional outcome measures occur while traveling to Cleveland VA Medical Center and Kessler Foundation/Kessler Institute for Rehabilitation, all Cleveland Clinic study staff will be re-trained to ensure standardization of methodology. By using this standardization plan, all study staff will be prepared to evaluate patients when we begin patient enrollment ~6 months after the clinical trial begins. MetroHealth Hospital team (Anne Bryden and Amy Friedl) will be trained on the standardized methodology during the first quarter of the fourth year (September 2021-November 2021).

- *Transcranial Magnetic Stimulation (TMS)*
  Dr. Plow has over a decade of experience in delivering TMS and training others in the delivery of TMS. In this study we will collaborate with other experienced researchers in the field of TMS; Dr. Yue (Kessler Foundation), Dr. Cunningham (MetroHealth Hospital) and Drs. Pundik and Baker (Cleveland VA). Drs. Yue and Plow were previous colleagues and collaborators at the Cleveland Clinic Foundation prior to Dr. Yue's transition to Kessler Foundation. At the Cleveland Clinic, Drs. Yue and Plow led and developed multiple protocols for TMS as is evident by their co-published articles [8-15]. Therefore, both Drs. Yue and Plow are well trained in identical methodology in TMS protocols and possess the same equipment to deliver TMS. Drs. Pundik and Baker are experts in TMS as well and have performed TMS studies with Dr. Plow for a number of years [1-3, 8, 11, 12, 16-22]. Therefore, the prior success of collaborations between Drs. Plow, Yue, Pundik and Baker for TMS studies indicates that standardization of TMS methodology across sites would not be difficult. All study staff will be trained by Drs. Plow, Yue, Pundik and Baker at each site, and standard operating procedures for TMS will be developed and distributed by Dr. Plow and Mr. Kyle O' Laughlin upon site visits within the first 4 months of the clinical trial in year 1. Dr. Cunningham was a previous student of Dr. Plow at the Cleveland Clinic, therefore the methodology of delivering TMS will be easily translated for this current trial. Dr. Cunningham and his team at MetroHealth Hospital will be trained during the first quarter of the fourth year (September 2021-November 2021).

- *Rehabilitation*
  Dr. Plow has worked with SCI patients for upper limb rehabilitation for over 4 years through her recent DoD-funded study [1-3]. Sample rehabilitation tasks from the previous pilot study will be dispersed between sites to aide in customization of therapy tasks for each patient, between physical therapists (Dr. Plow at the Cleveland Clinic, Ms. Garbarini at Kessler Foundation/Kessler Institute for Rehabilitation, Terri Hisel at MetroHealth Hospital and Ms. McCabe at the Cleveland VA Medical Center). In addition, study staff at each location involved in therapy will be trained by Dr. Plow on delivering rehabilitation based on massed-practice.

- *Transcranial Direct Current Stimulation*
  Dr. Plow has had over a decade of experience in using transcranial direct current stimulation (tDCS) to promote restoration of functional outcomes in applications ranging from vision to motor ability. With her experience, Dr. Plow has been able to optimize a dosage schedule for tDCS delivery for the proposed clinical trial using her previous pilot study. Therefore, since all the same equipment exists at all locations, during the first fiscal year site visit in month 4, Dr. Plow will advise Dr. Forrest, Dr. Pundik and Dr. Baker along with their respective research personnel how to properly apply the tDCS stimulation during rehabilitation.

It would be important to ensure consistency of dosing or treatment fidelity in application of rehabilitation. Safeguards are planned to ensure that all patients participating at all study sites receive the same dose of massed-practice rehabilitation for same length of time, with a similar ratio between tasks practiced with the weaker upper limb and those practiced with the stronger upper limb. Therefore, therapists at all sites, including the PI Dr. Plow at the Cleveland Clinic, Ms. McCabe at the Cleveland VA medical center and Ms. Garbarini at the Kessler Foundation/Kessler Institute for Rehabilitation will participate in Skype phone/video calls before starting treatment for any patient in the first year of the study. These meetings will allow every therapist to become more comfortable with dosage and frequency required for the proposed protocol. Therapists will have one additional meeting in the middle of the training regimen (session 7 or 8 out of 15) to ensure continued treatment fidelity. In years 2-4, therapists will have similar meetings for every other patient to ensure that even over several years, consistency of fidelity of rehabilitation delivery is maintained. Ms. Hisel at MetroHealth Hospital will be trained on administering tDCS by Dr. Plow and Mr. O'Laughlin during the first quarter of the fourth year (September 2021-November 2021).

2. DEVICE DESCRIPTION

2.1 Name of Device

This study will be conducted with the Soterix Medical 1x1 Low Intensity DC Stimulator. The Soterix Medical 1x1 Low Intensity DC Stimulator is an Investigational Device developed by clinical researchers, scientists, and biomedical engineers for use in clinical standard tDCS protocols.

2.2 Soterix tDCS Principle of Operation

For the specific steps on how to operate the Soterix Medical DC Stimulator, refer to the device manual.

Transcranial Direct Current Stimulation is treatment that utilizes electrode pads placed at opposing points on the scalp and a direct current stimulator to deliver electrical energy which transfer from the anode, across the scalp and skull, to the targeted location in the brain and then to the cathode placed at a different location on the scalp.

For the proposed indication, the aim is to deliver continuous bilateral transcranial direct current stimulation, directing the anode to the contralateral motor cortex of the more affected upper limb. The cathode will be placed on the ipsilateral orbit of the more affected upper limb. This will allow the current to flow from the motor hotspot (of the weaker muscle in the more affected upper limb) to its contralateral orbit.

2.3 Soterix tDCS System and TMS system Regulatory Status

The Soterix Medical 1x1 Low Intensity DC Stimulator is an investigational device. Federal (or United States) law limits device to investigational use. The intended use of the tDCS system used in this protocol is investigational.

The TMS System, Magstim Magnetic Stimulator and 70mm Double Coil is manufactured by Magstim Co. Ltd. These Devices have 510(k) Clearances for other intended uses. The intended use of the TMS system used in this protocol is investigational.

2.4 Proposed Indications for Use

The Soterix Medical 1x1 Low Intensity DC Stimulator will be used in this phase I/II clinical trial in combination with upper limb rehabilitation to improve functional outcomes and functional independence in individuals with chronic cervical spinal cord injury.

The TMS system, Magstim Magnetic Stimulator, will be used in this phase I/II clinical trial to record the neurophysiology in the Spinal Cord Injury population. This device will be used before the start of the treatment phase and at the end of the treatment phase to capture the changes in neurophysiology of this population.

2.5 Manufacturing information

Manufacturing information for the Soterix Medical 1x1 Low Intensity DC Stimulator is available on their website at soterixmedical.com
Manufacturing information for the Magstim 200^2 Magnetic Stimulator and Coil is available in Magstim Co. Ltd. Cleared 510k (K060847)

2.6 Labeling

The Soterix Medical 1x1 Low Intensity DC Stimulator and the TMS System to be used this clinical trial will bear a label with the following statement: "CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use."

3. BACKGROUND AND SIGNIFICANCE

3.1 Overview of SCI Epidemiology

Spinal Cord Injury remains a prominent cause of long-term disability. In the US alone, about 282,000 individuals are affected with SCI; over half of them are between the ages of 28 and 43. SCI is especially common among veterans, who constitute ~15% (42,000) of the injured population [1-4]. Since SCI affects a younger demographic, lifelong costs of disability are staggering. Direct lifetime burden can be up to $4.7 million per patient [2], while indirect costs can add another $701,000/year [5, 6]. This Clinical Trial seeks to offer cost-effective interventions that have the potential to reduce long-term disability in SCI.

3.2 Unmet Clinical Needs

Restoring motor function of the paretic upper limbs would address significant unmet clinical needs of patients with tetraplegia. Capacity to use the paretic upper limbs predicts functional independence and patients' subjective wellbeing. In a survey of 600 patients, up to 50% prioritized the return of upper-limb function over any other function lost after injury (fig. 1). Proportions were even higher among individuals with tetraplegia, of whom >75% reported the expectation for return of function of the upper limbs [8]. Our proposal seeks to offer interventions to restore motor function of the paretic upper limbs in tetraplegia to impact significant unmet clinical need.

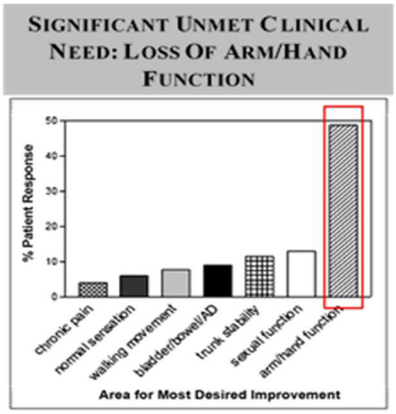

Fig. 1. SCI patients prioritize the return of arm/hand function more than any other function. (Adapted from Anderson, 2004.)

3.3 Current Standard of Care Approaches

Rehabilitation is the most common approach to restore motor function of the paretic upper limbs. According to the World Health Organization (WHO), "rehabilitation can [substantially] decrease the consequences of injury, improve health and quality of life and

decrease the use of health services…[over the long term]" [9]. Rehabilitation typically involves engaging the paretic upper limbs in exercise and practicing tasks simulating activities of daily living (ADLs) [10-16]. Benefits of rehabilitation, however, come slowly and are often insufficient. A minimum of 8 weeks of rehabilitation is required to elicit even modest improvement; >9 months are required to elicit clinically meaningful benefit [16, 17]. This Clinical Trial offers a simple, practical and inexpensive approach to enhance the outcomes of rehabilitation.

3.4 Enhancing Clinical Outcomes

Outcomes of rehabilitation remain limited because neural resources that survive SCI cannot effectively contribute to recovery [18-22]. Motor cortices and the emergent descending pathways (that survive in >65% of injuries, called "incomplete" SCI [23, 24]) demonstrate injury-induced imbalances in excitability. These substrates come to represent muscles spared above the level of injury and lose control of weak muscles affected below that level. Therefore, surviving neural resources are "taken over" by muscles spared above the level of injury, which leaves little opportunity for representation of weak muscles affected below that level [22, 38]. Weak muscles as such continue to weaken in the absence of rehabilitation/re-training [20, 27, 33, 35-37,39]. Although rehabilitation can help restore excitability of surviving neural resources devoted to weak muscles, these plastic changes are insufficient to dramatically affect their contribution towards recovery [40-44]. Therefore, here, we test the scientific premise that delivering electrical stimulation to motor cortices and residual descending pathways during rehabilitation would generate greater restoration of excitability and enhance their contribution towards recovery.

Evidence generated from hundreds of studies, including our own work, has especially highlighted the promise of tDCS. Findings from our work have revealed that tDCS delivered to the motor cortices and the residual corticospinal pathways can elicit promising improvements in rehabilitative outcomes of the paretic upper limb in patients with neurologic diseases like stroke. A four-fold greater improvement in motor function can be generated by adding positive (anodal) tDCS during rehabilitation. Mechanisms entail increase in excitability of motor cortical maps and residual corticospinal pathways devoted to the weak muscles [46-58].

3.5 Innovation

This clinical trial will be the first study to test the effectiveness of multiple sessions of tDCS in individuals with SCI. Study of the use of tDCS in SCI is in the elementary stages compared to the evidence available in the field of stroke or other neurologic injuries [45, 52]. Only a handful of studies have explored the effects of tDCS upon restoration of upper-limb motor function, and even then only short-term effects, based on the application of single sessions, have been studied [69-72]. Our recently published DoD-funded pilot study was the first study in which tDCS was given for multiple sessions in rehabilitation of SCI individuals [61]. Though another group had adopted a similar design, they had paired tDCS with an investigational treatment (robotic therapy) not clinical rehabilitation [73, 74]. Therefore, our proposed study will be the first efficacy trial to report upon the functional benefits of combining tDCS with clinical rehabilitation for multiple sessions in SCI. As such, our design carries more clinical relevance and has the potential to generate longer-lasting functional benefits than contemporary studies.

3.6 Significance

The approach of noninvasive brain stimulation is, we believe, a simple, safe, and affordable technique to restore upper-body function after SCI. This method can be delivered during standard rehabilitation, with no need for additional time or resources; it has the potential to become an easily applied, cost-effective, practical tool that can easily be offered at a number of sites. Also, since our evidence indicates that this technique can help generate promising gains in rehabilitation within a short time, it also has the potential to substantially reduce the costs of managing disability in SCI.

4. REPORT OF PRIOR INVESTIGATIONS

4.1 Summary of Previous Studies

Our recent published and preliminary work funded by the DoD and the Conquer Paralysis Now foundation indicates that tDCS can be effective for enhancing rehabilitative outcomes in SCI [59-62]. In a pilot, randomized, double-blinded, placebo-controlled clinical trial, we allocated 14 patients with C2-C6 incomplete SCI (≥1year post injury; having sparing to muscles in the upper extremities below the level of injury) to either receive tDCS (n= 8) or sham tDCS (n= 6) during rehabilitation. Interventions were given for 2 hours/day, 5 days/week for 2 weeks. Before receiving these interventions, patients completed a baseline control phase lasting 2 weeks, during which they continued with the typical routine. After receiving the interventions, patients completed a 3-month follow-up phase, during which they engaged in a home exercises prescribed by the physical therapist (PI, Plow).

Outcomes included metrics specified in the Common Data Elements (CDEs), developed through the collaboration of the International Spinal Cord Society, the AIS, and the National Institute of Neurological Disorders and Stroke (NINDS). The primary outcome was the Upper Extremity Motor Score (UEMS), which rates power/strength of 10 muscles of the arm and hand, each on a 0-5 scale of the UK's Medical Research Council (MRC; 0, no voluntary twitch; 5, maximum contraction against resistance). The sum total ranges between 0 and 50. The secondary outcome was fine-motor control or dexterity tested using the Nine-Hole Peg Test (NHPT), which requires patients to place tiny pegs into holes on a board, then remove and replace them as quickly as possible. Neurophysiologic metrics were also collected, with the use of TMS. Excitability of motor cortical maps and residual corticospinal pathways was quantitated for strong muscles above the level of injury (C3-C6) and weak muscles below that level (C6-T1).

Our results, published in *Spinal Cord* and *Journal of Spinal Cord Medicine,* have revealed several noteworthy findings in line with the aims of the proposed study [60-62]. Regarding Aim 1, results of our pilot study have revealed that patients receiving tDCS during rehabilitation show twice as much gain in strength of the muscles of the weaker upper limb than patients receiving rehabilitation alone (4- vs. 2-point gain on UEMS) ($t_{7,\ 0.05}$ = 7.3, $p < 0.0001$). Gains are maintained even 3 months after the completion of tDCS ($t_{4,\ 0.05} = 3.1$, $p < 0.018$). Gains are particularly evident for muscles innervated below the level of injury (C6-T1). Greater number of muscles innervated below the level of injury shows clinically detectable improvements in strength after tDCS (≥1 full muscle grade increase on MRC [63, 64]) ($t_{10,\ 0.05} = 1.55$, $p = 0.07$). Triceps muscle (C7), one of the most functionally important muscles for performing transfers, for instance, improves by 1-full muscle grade on average after two-weeks of tDCS (clinically detectable gain) ($t_{6,\ 0.05} = 3.33$, $p < 0.008$). Improvements witnessed for strength translate to improvements in dexterity ($t_{12,\ 0.05} = 1.84$, $p = 0.045$). Improvements

witnessed with rehabilitation alone, however, remain less remarkable (<0.5 muscle grade increase on MRC) ($t_{4, 0.05} = 2.14$, $p = 0.05$).

In accord with the proposed Aim 2, patients receiving tDCS during rehabilitation show greater gains in excitability of the brain and the residual descending pathways devoted to weak muscles. Although at baseline, patients show a greater number of excitable brain sites devoted to the stronger than the weaker muscles, in line with findings of injury-induced imbalances in excitability reported in earlier preclinical and clinical studies ($t_{7, 0.05} = 1.82$, $p = 0.05$) [20, 26-31], after tDCS, balance tends to become restored. The number of brain sites devoted to the stronger muscles tends to decrease ($t_{6, 0.05} = 1.07$, $p = 0.16$), whereas that devoted to the weaker muscles tends to increase after tDCS ($t_{6, 0.05} = 1.43$, $p = 0.1$) (fig. 4A, D). What is equally compelling is that such re-balancing is not witnessed after rehabilitation (without tDCS); instead, patients show further increase in the number of brain sites devoted to the strong muscles ($t_{4, 0.05} = 1.84$, $p = 0.07$). Therefore, the ratio of weak vs. strong muscle map in the motor cortices shows larger gains after tDCS than after rehabilitation, i.e., the ratio or the balance shifts in favor of the weak muscles ($t_{10, 0.05} = 1.92$, $p = 0.08$). Restoration of balance is associated positively with gains in strength of the weak muscles. Patients who show the greatest gain in the number of brain sites devoted to weak muscles also experience the greatest gains in strength of those muscles. Thus, tDCS helps re-balance or restore the excitability of surviving neural resources, plasticity that is functionally adaptive.

Regarding Aim 3 of the proposed study, patients receiving tDCS during rehabilitation experienced no serious adverse events. Further, these patients were not any more likely to guess which group they were in compared to patients who received sham tDCS ($X^2 = 0.69$; p= N. S.). Thus, overall, the application of tDCS during rehabilitation is safe for individuals with SCI based on the findings of our pilot study. Our study also shows that it is feasible to test tDCS against a placebo condition in the proposed randomized, sham-controlled, double blind, phase I/II safety-efficacy clinical trial.

4.2 Conclusion

In general, results of our pilot study indicate that tDCS is a promising technique to enhance rehabilitative outcomes of the paretic upper limbs in patients with incomplete cervical SCI [60, 61, 65]. Effects of tDCS are related to mechanisms of restoration of balance in excitability– re-mergence of the brain representation of weak muscles and reduction of the brain representation devoted to spared, strong muscles within residual neural resources. What speaks to the scientific rigor of our findings is the evidence that effects of tDCS observed here cannot be explained based on spontaneous shifts in function or excitability, or test-retest effects. Metrics of strength and dexterity and those indexing neurophysiology remained stable in the absence of any intervention. Values of UEMS and TMS metrics showed excellent and moderate-to-excellent reliability during the baseline control phase (concordance correlation coefficient [CCC] = 0.964, and CCC= 0.644 to 0.935, respectively) [60]. Therefore, greater confidence can be placed upon the findings demonstrating promise of tDCS during the intervention phase. Here, our objective is to investigate whether the promise of tDCS, and the mechanisms underlying its effect, observed in our recently published single-center pilot study can be replicated by performing the study at other multiple centers [60, 61, 65]. A multi-center investigation is a natural, logical progression to establish the generalizability of the effect of tDCS across different types of patients and confirm the validity of our findings.

5. STUDY DESIGN

5.1 Study Objective

The objective of the proposed trial is to extend the scope of our pilot study and conduct a phase I/II multi-site randomized controlled, double-blinded clinical trial to test the safety, feasibility, efficacy, and mechanisms of delivering tDCS with rehabilitation in SCI. At least forty-nine (up to 54) patients with chronic, incomplete (having sparing to muscles in the upper extremities below the level of injury) C1-C8 SCI will be enrolled across 4 sites: Cleveland Clinic (at least 21[up to 25] subjects), Kessler Foundation/Kessler Institute for Rehabilitation (14 subjects), Cleveland VA Medical Center (6 patients), and MetroHealth Hospital (8 patients). Patients will first complete a baseline control phase lasting 3 weeks, during which they will continue with their typical routine and activities (fig. 4). After the baseline control phase, they will be randomly assigned to either receive tDCS ($n = 22$) or sham tDCS ($n = 22$) during rehabilitation. Rehabilitation will be given for 2 hours/day, 5 days/week for 3 weeks. Rehabilitation will especially involve exercises for weak muscles innervated below the level of injury, such as triceps (C7). After the completion of the rehabilitation/intervention phase, patients will participate in a 3-month follow-up phase, during which they will be asked to continue with exercises prescribed as part of the home-exercise routine. Up to 42 age matched healthy control participants will also be enrolled to record 'normal' neural indices (15 at the Cleveland Clinic, 6 at Kessler Foundation, 6 at Cleveland VA, and up to 15 at MetroHealth Hospital).

Assessments will be completed before and after the baseline control phase (pretests 1/2), the intervention phase (posttest) and the 3-month follow-up phase (follow-up) (fig. 4). Assessments will include metrics of strength and dexterity (Graded Redefined Assessment of Strength, Sensation and Prehension [GRASSP]); functional abilities (Wolf Motor Function Test [WMFT]); activity limitations (self-care subscale of the Spinal Cord Independence Measure [SCIM]); and participation restrictions (Canadian Occupational Performance Measure [COPM]). TMS will be used to study excitability of neural resources devoted to a weaker muscle and a spared muscle. The Hoffmann reflex (H-reflex) involving peripheral electrical stimulation will be used to study spinal excitability. Up to 42 age-matched (±5 years), healthy control subjects will also undergo testing of TMS/H-reflex at a cross-sectional time-point. The goal will be to establish age-based norms for neurophysiologic metrics related to non-dominant biceps and triceps muscles. In accordance with feedback provided by DoD reviewers, adverse effects, SCI-specific symptoms (e.g., pain, autonomic dysreflexia) and attrition and integrity of blinding will also be recorded. The following aims and hypotheses will be tested in the proposed study.

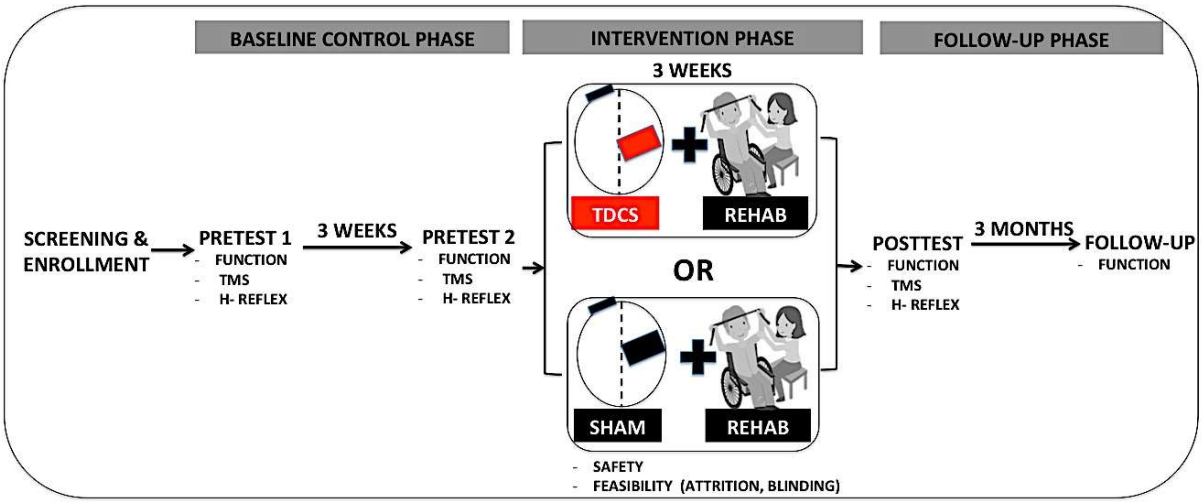

Fig. 4: Study Design and follow-up procedures. TMS= Transcranial Magnetic Stimulation; H-reflex= Hoffman Reflex; tDCS= transcranial direct current stimulation (tDCS)

5.2 Sample Size Estimation and Power Analysis

Table 2: Sample Size Estimation based on Power Analysis

	Outcomes/Metrics	Effect size (tDCS vs. Sham)	α	80%	85%	90%	95%
Aim 1	UEMS (# Weak muscles showing clinically detectable improvement)	0.938	0.05	40	44	52	62
	Δ% Nine Hole Peg Test	1.033	0.05	32	36	42	52
Aim 2	Δ% Map Ratio (Weak map/Strong map)	1.192	0.05	26	30	34	40

Sample size was calculated based on PI Dr. Plow's recent DoD-funded pilot study [60, 61]. Differences in effect size between tDCS-+-rehab and sham-+-rehab groups were used to estimate sample sizes, based on two sample t statistics compiled at $\alpha = 0.05$ for 80% power (Table 2). For Aim 1, data concerning strength/power of muscles and dexterity (NHPT) was used since both of these metrics are components of the primary outcome for Aim 1 (GRASSP). Based on between-group comparison of the numbers of weak (C6-T1) muscles that achieved clinically detectable improvements on MRC (≥1 full grade gain [63, 64]), we would require a total of 40 patients, and based on between-group comparison of % improvement on the NHPT (pegs per second), we would require 32 patients for achieving 80% power. This estimate would be sufficient for Aim 2 as well. For Aim 2, data concerning motor cortical map excitability was used, as this is the primary outcome for Aim 2. Based on between-group comparison of % change in map ratio (weak map/strong map), we would require 26 patients for achieving 80% power. Considering that there could be attrition of 10%, we expect to enroll 44 patients. A sample of 44 patients with 22 patients included in each SCI group would also be sufficient for study of Aim 3, which is designed to show that tDCS-+-rehab is at least as safe and feasible (no greater attrition or probability of guessing the group) as rehabilitation given alone (sham-+-rehab).

5.3 Primary Endpoint

EFFECTIVENESS OF PAIRING TDCS WITH REHABILITATION. *Hyp. 1:* Patients receiving tDCS with rehabilitation will achieve greater gains in strength and dexterity, with reduction in activity limitations and participation restrictions, than those getting rehabilitation alone. Responders/non-responders will be identified

based on baseline clinico-demographic characteristics, such as the level of injury, degree of incompleteness and time post-injury, etc.

5.4 Secondary Endpoints

MECHANISMS OF PAIRING TDCS WITH REHABILITATION. *Hyp. 2:* Patients receiving tDCS with rehabilitation will exhibit larger gains in excitability of neural resources devoted to the weak triceps muscle (C7) and greater reductions in excitability of neural resources devoted to the spared biceps muscle (C5) compared with patients receiving rehabilitation alone. Patients receiving tDCS in rehabilitation will also exhibit larger gains in spinal excitability. Relationship between neural mechanisms and gains in strength and dexterity and functional abilities will be explored.

SAFETY AND FEASIBILITY OF PAIRING TDCS WITH REHABILITATION. *Hyp. 3:* Patients receiving tDCS with rehabilitation will show no greater adverse effects or attrition or ability to correctly guess the group allocation than those receiving rehabilitation alone.

6. SUBJECT SELECTION

6.1 Study Patient Population

Subjects participating in the study will be medically stable individuals who have been diagnosed with incomplete cervical spinal cord injury over 1 year ago and continue to have difficulties using one or both of their upper limbs. Subjects will be selected to participate in the study based on the inclusion/exclusion criteria listed below. Subjects will not participate in any study-specific tests or procedures before their written informed consent.

6.1a General Inclusion Criteria

Patients with incomplete (having sparing to muscles in the upper extremities below the level of injury) C1-C8 SCI; age ≥18 years; ≥1 year time post injury (to avoid confounding effect of cervical root recovery [77]) will be enrolled. On the more affected side, patients will be required to have sparing of either the biceps or the triceps muscle, defined as ≥3-muscle power grade on the MRC scale. They will also be required to show weakness of the muscle antagonist to the spared muscle i.e. triceps in case of spared biceps, or biceps in case of spared triceps on the affected side. Weakness will be defined as a MRC grade of 1-3, and a clinically detectable difference in power compared to the power of the spared muscle, i.e., ≥1 muscle grade lower on the MRC scale [63, 64]. Criteria requiring sparing of one muscle and the weakness of the antagonist muscle are meant to create a homogeneous sample for the study of neurophysiology using TMS in Aim 2. These criteria will not be limiting for subject recruitment, as evident from the successful completion of our recent pilot work, because patients with cervical SCI either commonly show sparing of biceps (C5) and weakness of triceps muscles (C7), or this order of weakness is reversed in patients with central cord syndrome [60, 61]. On the contrary, these criteria will allow inclusion of even more-impaired individuals, who may not have "active hand function" as required by typical SCI studies [66, 68] and an ongoing study (NCT02611375).

6.1b General Exclusion Criteria

Patients with contraindications to tDCS and TMS, including pacemaker, metal in the skull, seizure history, or pregnancy will be excluded [75, 77]. Patients with spine stabilization will be included because the site of TMS/tDCS application to the head is distant from the site of the metal implant in the neck. Patients on an anti-spasticity or pain medication regimen will also be included, as long as the same dose and regimen are maintained. Patients with active pressure ulcers, however, will be excluded to avoid disruption of ongoing medical treatment. Patients with traumatic brain injury (TBI), diagnosed based upon acute injury Rancho scale <5 or positive MRI/CT findings at the time of injury will also be excluded to prevent confounding of TMS metrics. Patients with excessive tone/spasticity (Modified Ashworth Scale [MAS] >3) and severe contractures or soft tissue shortening at elbow/wrist will be excluded. Finally, patients participating in ongoing upper-limb therapies will be excluded to minimize the possibility of confounding effects. For healthy control participants, the exclusionary criteria will be the same as mentioned above. Healthy control inclusion criteria is age between 18-70 years old, without any diagnosis of neurological disease.

6.2 Subject Recruitment

Patients will be recruited via methods found successful in the PI's recent pilot trial (NCT01539109), funded by the Department of Defense. Patients will be recruited from 9 area hospitals within the Cleveland Clinic, from outpatient and community-based programs, support groups, and referrals. We will also enroll directly from Cleveland Clinic Physician Dr. Greg Nemunaitis. Dr. Nemunaitis is new to the Cleveland Clinic, however he has held the largest practice for SCI in NE Ohio for decades. Therefore, his patients who visit him at CCF will serve as the ideal candidate population. Dr. Nemunaitis and the Research Personnel will tell his patients about research studies when they arrive for their exam visit. Enrolling past trial participants will also prevent delays in enrollment. Those on the Pilot study's waiting list could be contacted for the proposed study. Subject recruitment will be significantly enhanced through the use of Cleveland Clinic's KP, which logs each neurological outpatient visit within Cleveland Clinic and therefore provides valuable long-term and follow-up information, aiding in study recruitment. KP will be used to request a list of potential participants. KP generates a list of patients seen at a particular center at the Cleveland Clinic that can be filtered by certain center metrics. We will send KP request to centers at the Cleveland Clinic that have been known or are suggested to us by site physicians at location on campus that SCI patients are seen. KP then will send us the password protected list and we will save on our private server with a password protection only know to lab personnel. Patients of the KP query that seem to be a potential fit will have a letter sent to their physician to see if we can contact their subject in regards to our study and potentially screen. Another recruitment method we will adopt is the use of eResearch and an EPIC heat request. eResearch Requests allows us to request patient MRN's from the Cleveland Clinic medical records system that fit a certain criteria that we provide. From this request we will be receiving monthly excels from the eResearch team with the names of individuals which fit the request filters we initially provided to them. Epic Heat requests will allow us the ability to request a report of patient MRNs from the EPIC team based on a set criteria for participants to fit are inclusion criteria. We will save these Excel sheets sent to us by the respective teams as password protected documents and review the MRNs through our usual

chart review method. After subjects are identified we will following our usual route of contacting subjects which involves sending physician letters via email or EPIC Messaging, then send the patient letters via physical postal mail or EPIC Messaging/MYCHART to those patients that physicians do not say no to sending a letter, and then calling the potential participants after 1-2 weeks to gauge their interest in participating if they do not call us first.

In addition, we will be working with our partners at Select Medical to identify potential candidates housed in their acute rehab hospitals (Edwin Shaw, Avon, and Beachwood) and provide study fliers/brochures to them via intake binders or advertisements placed at the facilities. It is anticipated that these patients in Select Medical CCF acute rehabilitation hospitals will not meet the 1 year post-cervical spinal cord injury inclusion criteria for the study, however, providing these potential participants with our study information may help give the patients an idea of what avenues they can pursue upon completion of their clinical care. As a preparatory step in research, if an interested candidate reaches out to us, we will perform phone screening even though they will not meet our time post injury criteria. This will allow us to identify any immediate exclusionary criteria related to the study protocol and provide input to the interested candidate on their potential for participation after their clinical care.

Dr. Plow has also created links with the many agencies and support group for SCI survivors across Ohio, on which she has relied or help with patient recruitment.

We also will potentially use the following for posting advertisements in the region and nationwide: National Spinal Cord Injury Association Newsletter, Publications of the Paralyzed Veterans of America, Local Newspapers, Posting the clinical trial on SCOPE (www.scope-sci.org), nationally on clinicaltrials.gov.

A Brochure and flyer will also be used to advertise for the study.

6.3 Subject Screening

SCI physicians at each site (Dr. Bethoux at Cleveland Clinic; Dr. Richmond at Cleveland VA Medical Center; Dr. Kirshblum at Kessler; Dr. James Wilson at MetroHealth Hospital) will screen patients at the beginning of the study to determine eligibility, either on-site or through a video screen for subjects who cannot reasonably make it to one of the sites. International Standards for Neurological Classification of SCI (ISNCSCI) will be used to confirm the diagnosis, the degree of completeness of injury (AIS A, B, C, or D), and zones of partial preservation below the level of injury. Strength or muscle power will be recorded using UEMS to identify the weaker upper limb. Physicians will quantify spasticity using the MAS and note any tightness and contractures. Complaints of neuropathic pain and autonomic dysreflexia will be noted. Medication usage will be screened and documented. Physicians will examine patients and exclude those with active pressure ulcers. Physicians will also determine whether patients had suffered an associated TBI at the time of SCI. A diagnosis of TBI will be made based on original radiographs and clinical records, as well as history and physical examination. Patients who are found to have had a Rancho Los Amigos Scale score of level V or below, and/or any MRI- or CT-evidence of focal cerebral cortex involvement or hydrocephalus from the time of injury, and/or history of (non-sedated) post traumatic amnesia lasting >48 hours, will be excluded. ISNCSCI, medical history and physical

examination are considered part of the NINDS CDEs for SCI. Therapists will also conduct a screening to assess upper limb functionality before subjects are enrolled. This is done on-site before or after the physician screening, unless subjects are not within a reasonable distance to the Cleveland Clinic and a virtual visit is more appropriate.

6.3 Subject Enrollment

A subject is enrolled in the study after they have provided informed consent. The subject also has to meet all of the inclusion and none of the exclusion criteria determined by the site PI.

7. STUDY VISITS

7.1 Study Schedule

Figure 2 below provides a study flow diagram from the point of subject screening and consent through the final follow-up visit.

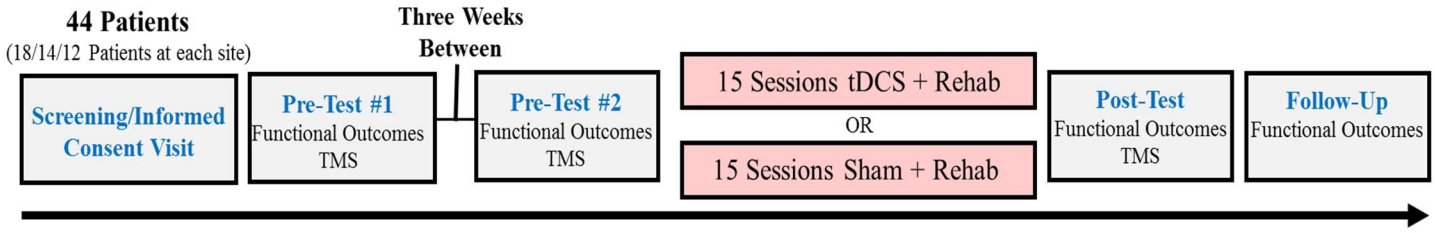

Fig.2

7.1a Schedule of Study Visits

Study Phase	Visit	Schedule
Screening/ Informed Consent	The screening/informed consent visit will occur with a single on-site visit or if necessary, an additional video screening before the on-site screening. After informed consent, screening functional tests will be performed.	1 on-site visit and a potential video screen
Baseline Rehab Functional and Neurophysiology Testing	Pre-Test #1 will involve functional tests and Neurophysiology (TMS, H-Reflex) tests. The visits will occur over 2 days and last 8-11 hours. Pre-Test #2 will involve functional tests and Neurophysiology (TMS, H-Reflex) tests. The visits will occur over 2 days and last 8-11 hours.	2 on-site visits (any day after informed consent/screening visit) 2 on-site visits (at least 3 weeks after Pre-test #1)
Rehab Phase	15 visits of rehab. During rehab visits subject will have SHAM or REAL tDCS administered. Each rehab session will last for 2 hours.	15 on-site visits. (5 times per week for 3 weeks)
Post-Rehab Functional and Neurophysiology Testing	Post-Test will involve functional tests and Neurophysiology (TMS, H-Reflex) tests. The visits will occur over 2 days and last 8-11 hours	2 on-site visits (within 1 week after the final rehab visit)

3 Month Follow-up Testing	Follow-up will involve functional tests. This visit will last between 1-3 hours. Optional Neurophysiology testing (TMS, H-Reflex)	1 on-site visit, (OPTIONAL: +1 on-site visit) (3 months after the final rehab visit)
6 Month Follow-up testing (OPTIONAL)	Optional Follow-up will involve functional tests and Neurophysiology (TMS, H-Reflex)	2 on-site visits (6 months after the final rehab visit)
12 Month Follow-up testing (OPTIONAL)	Optional Follow-up will involve functional tests and Neurophysiology (TMS, H-Reflex)	2 on-site visits (12 months after the final rehab visit)

7.1b Schedule of Study Assessments

Schedule of Study Assessments

	Preliminary Screening	Informed consent/ Formal Evaluation	Pre-Test #1	Pre-Test #2	Rehabilitation															Post-Test	3-month Follow-Up	3-month Follow-Up (OPTIONAL)	6-month Follow-Up (OPTIONAL)	12-month Follow-Up (OPTIONAL)
					1	2	3	4	5	6	7	8	9	10	11	12	13	14	15					
phone screening document	x																							
Inclusion/Exclusion		x																						
ASIA Classification		x																						
Upper Extremity Motor Score(UEMS)		x																						
MRC Muscle Strength Scale		x																						
Spinal Cord Independence Measure(SCIM)			x	x																x	x		x	x
Canadian Occupational Performance Measure (COPM)			x	x																x	x		x	x
GRASSP			x	x																x	x		x	x
Neurogenic Bladder Symptom Score (NBSS)			x	x																x	x		x	x
Modified Ashworth Scale (MAS)			x	x																x	x		x	x
Capabilities of Upper Extremity Test (CUE-T)			x	x																x	x		x	x
Transcranial Magnetic Stimulation (TMS) Neurophysiology Tests			x	x																x		x	x	x
H-Reflex			x	x																x		x	x	x
TMS Adverse Effects Questionnaire			x	x																x		x	x	x
vital signs(blood pressure, heart rate, respirations, blood oxygen saturdation)			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
tDCS Adverse Effects' Questionnaire					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x					

Fig.3

7.2 Baseline TMS and Functional Testing

Patients found to be eligible after screening will be tested on pre-test 1 and pre-test 2 (fig. 2). Both pre-test 1 and pre-test 2 will be conducted over 2 days lasting 8-11 hours (1 day functional testing, 1 day neurophysiology testing). They will be asked to continue with their typical routine and activities during what will be called the baseline control phase, lasting for 3 weeks. Patients will be asked specifically to refrain from participating in new training regimens involving the paretic upper limbs. During the Baseline Control Phase subject will participate in 2 Pre-testing visits. During each pre-test visit subject will undergo functional tests and Neurophysiology tests as seen in figure 3. There will be a 3 week break period between each pre-test visit (pre-test visits 2 should be at least 14 days after pre-test visits 1).

7.3 Rehabilitation with tDCS

Each subject with SCI will perform rehabilitation while receiving tDCS (randomly assigned active or sham stimulation) for 15 total visits.

7.3a Rehabilitation

Patients in both groups will receive 15 sessions of rehabilitation delivered for 2 hours a day, 5 days a week, for 3 weeks. Rehabilitation will be prescribed by site physical therapists: the PI Dr. Plow at Cleveland Clinic; Ms. Garbarini at Kessler; Ms. Jessica McCabe at Cleveland VA Medical Center; and Ms. Hisel at MetroHealth Hospital. Rehabilitation will be based on the principle of massed practice [17, 66, 67]. Massed practice involves intensively engaging the paretic upper limbs in 10-15 tasks. Massed practice has shown promise at reducing the weakness of the upper limbs in our recent study and studies by other groups [17, 61, 66, 67].

Training of the weaker upper limb will be emphasized with massed practice. Training of the weaker upper limb is more functionally relevant than training of the stronger one. In addition, training of the weaker upper limb will also maximize the potential of restoring function with tDCS. tDCS will be delivered using the typical uni-hemispheric montage, i.e., targeting the hemisphere contralateral to the weaker limb. The weaker upper limb will be identified based on patient report and UEMS collected at screening. About 80% of the tasks will engage the weaker upper limb, while remaining tasks will engage both limbs.

Tasks will be chosen based on the patient's preference and priority for achieving functional independence and will be designed so as to maximize the transfer to performance of real-world activities. Similar to practices commonly used in rehabilitation clinics, tasks will primarily engage muscles innervated below the level of injury (C6-T1). Engagement of the weak triceps (C7) will be especially emphasized, for instance, through activities like rising from a chair while pushing on armrests, or reaching for different targets positioned on a tabletop. Return of triceps strength is functionally relevant because triceps is critical for performing transfers to and from the wheelchair/surfaces and reducing caregiver assistance.

Each task will be performed 10 times and will be repeated if deemed necessary. Performance metrics like speed, accuracy, number of trials completed, etc., will be recorded and tracked. Feedback will be provided. Tasks will be made more (or less) challenging as patients recover movement abilities [76, 79]. Patients will also be asked to practice the tasks at home for 30 min a day, 5 days a week, for 3 weeks. Adherence to home exercises will be monitored using a home-exercise log that will be shared with investigators at every training session.

7.3b tDCS

Transcranial Direct Current Stimulation (tDCS) will be delivered using a 9-V battery-operated device (Soterix Medical, New York, NY). Surface electrodes will be placed inside saline-soaked sponge inserts (5x7 cm^2) and applied to different regions on the scalp. The anodal electrode will be applied over the primary motor cortex, contralateral to the weaker upper limb. The center of the electrode will be positioned at a site evoking the largest muscle potentials in weak triceps using TMS (details follow). Location of the rectangular electrode (four corners and center) will be marked using stereotactic navigation. An overlap of the electrode locations will be generated for the 15 sessions to establish reproducibility. The cathodal electrode will be applied over the opposite supra-orbital area.

Current will be delivered at a dose of 2mA. Currents will be delivered for the first 30 minutes of the first hour of rehabilitation and the first 30 minutes of the second hour of rehabilitation for each rehab session. Sham tDCS

will be delivered using the same application, but currents will be ramped up slowly at the beginning and ramped down slowly at the end. This sham technique facilitates blinding of the subject.

7.4 Post TMS and Functional Testing

Post rehabilitation TMS and Functional testing will happen within the week of finishing rehab visit 15. During the Post TMS and Functional testing visit, subject will undergo the same testing that occurred during pre-testing visits 1 and 2. The functional tests and neurophysiology (TMS) testing that the subject will undergo can be seen in figure 3.

7.5 Long term Follow-up

After the posttest, patients will continue to engage in a home-exercise program prescribed by the site physical therapist. Patients will be expected to perform exercises for 30 min/day, 5 days/week, for 3 months. Adherence will be monitored using exercise logs, similar to those used during the intervention phase. Patients will receive monthly phone calls from study coordinators from respective sites (Mr. O' Laughlin from Cleveland Clinic, Ms. McCabe from Cleveland VA Medical Center, Ms. Martinez from the Kessler, and Ms. Amy Friedl from MetroHealth Hospital sites). During these calls, exercise logs will be reviewed, questions/concerns will be addressed, feedback about performance will be provided, and tasks will be made more (or less) challenging if necessary, based on direction from the site physical therapists [76, 79]. After follow-up, patients will return to their respective study site for testing of function (fig 3).

7.5A OPTIONAL Long term Follow-Up

Optional long term follow-up visits at 3(Optional Neurophysiology) and/or 6 and/or 12 months will be performed on select patients to monitor longer term changes in chosen patients who have opted into the extended long term follow-up. During the long term follow-up patients will not be expected to perform the exercises given after the completion of the intervention. Also Phone calls will not be made during this time. We will ask patients to continue to work on exercises for the more affected limb and allow them to call us with any questions or input to their home exercise routine. Subjects will not be limited from participating in any clinical procedures during this time as well. At 3(Optional Neurophysiology) and/or 6 and/or 12 months the chosen subjects who opted in at the time of consent will come back into the clinic to perform 1 day of functional testing and 1 day of neurophysiology testing as was done at post-testing.

7.6 Healthy Control Study Visit.

Healthy controls that are enrolled in the study will come in for one site visit. The site visit will involve TMS neurophysiology testing, identical to Pre-test 1 that patients perform (fig 3). The time involved in study procedures for healthy controls is approximately 4-6 hours.

8. SAFETY REPORTING

8.1 Definitions and Classification

The following definitions are from Good Clinical Practice (ISO 14155:2011) and FDA Code of Federal Regulations for Medical Devices (21 CFR 812.3(s)).

8.1a Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

AE includes all hospitalizations and events related to the investigational device or the comparator. This Includes events related to the procedures involved (any procedure in the clinical investigation plan). For users or other persons this is restricted to events related to the investigational medical device.

AE does not include conditions pre-existing to the subject's enrollment. Pre-existing conditions will not be reported as AEs unless the condition has an increased occurrence or intensity.

8.1b Serious Adverse Event (SAE)

An SAE is any AE that:

a. led to a death
b. led to a serious deterioration in health that either:
    i. resulted in a life-threatening illness or injury,
    ii. resulted in a permanent impairment of a body structure or a body function,
    iii. required in-patient hospitalization or prolongation of existing hospitalization,
    iv. resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,
    v. resulted in a substantial disruption in ability to conduct normal life functions.

SAE does not include in-patient hospitalization for a planned study procedure. Planned study-related in-patient hospitalization is not an SAE.

SAE includes device deficiencies that might have led to a serious adverse event if (a) suitable action had not been taken or (b) intervention had not been made or (c) if circumstances had been less fortunate. These are handled under the SAE reporting system. A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health or to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, is not considered to be a serious adverse event.

8.1c Relatedness to Study Procedures

The probability that a particular AE is related to any of the study procedures shall be coded on the AE case report form as *unrelated*, *possibly related*, or *related*. Probability ratings are based on the temporal relationship to the intervention, the likelihood that the symptom could have been produced by the participant's clinical state, the environment or other interventions, whether the participant's symptom course follows a known pattern of response to the intervention, and the experience and judgement of the lead investigators at each site.

9. DATA MANAGEMENT

9.1 Identifiers and Code System

All patients will be given an identification code at first contact with the study. This identifier will be unrelated to any aspect of subject's protected health information (PHI). Each site will have a unique identifier system consisting of a letter related to the specific study and a random 3-digit number. All study data will be de-identified and only the study identification code system will be followed.

9.2 Completion and Storage of Case Report Forms

To ensure data quality and completeness, all required study data shall be recorded on case report forms (CRFs). Hard-copy version of study-related data will be kept separate from identifiable information in a locked cabinet. All electronic data will be backed up on a separate secure server to ensure data protection. As stated earlier, Cleveland Clinic, Cleveland VA Medical Center, Kessler foundation/Kessler Institute for Rehabilitation, and MetroHealth Hospital provide secure servers to each laboratory to help save and back-up de-identified electronic study data. On these secure servers and on laboratory's authorized computers, electronic data will be kept in a folder available only to the researchers named and authorized at each site. Authorized individuals would access this data on their respective laboratory-based computers for which their use is authorized and monitored. Each site will be responsible for the storage of its own data and identifiable information. Hard-copy data will be verified by two independent evaluators before it is entered electronically. At each site, study-related data will be kept for seven years from the date of application to the IRB and the Human Subject Research Protection Office (HRPO) (GLP), based on Good laboratory practices (GLP) (21CFR 58). Data will be stored on laboratory's authorized computers and any hard-copy data would be converted to electronic data with REDCap capture. The Cleveland Clinic, Kessler Foundation/Kessler Institute for Rehabilitation, Cleveland VA, and MetroHealth Hospital will all be adding data to the Cleveland Clinic REDCap system. Study Personnel from each site will be granted access to REDCap to enter the data and CRF's into the Cleveland Clinic REDCap. During this time, only the principal investigator, study coordinator and authorized study staff will have access to the Cleveland Clinic computer that would be password-protected and locked for access. The database will be password-protected and backed-up to ensure that data integrity is maintained.

9.3 Confidentiality

At the beginning of the study, a physician-confirmed diagnosis of spinal cord injury (SCI) is important. For this, medical records, MRI, and radiology reports will be requested from patient's physician/hospital through written approval. Following the process of informed consent, the SCI physician for each site, Dr. Bethoux (Cleveland Clinic), Dr. Kirshblum (Kessler Foundation/Kessler Institute for Rehabilitation), Dr. Richmond (Cleveland VA Medical Center), and Dr. James Wilson (MetroHealth Hospital) will screen patients. Rehabilitation evaluation will be completed by SCI physical therapists: Dr. Plow at the Cleveland Clinic, Ms. McCabe at the Cleveland VA Medical Center, MS. Garbrini at Kessler Foundation/Kessler Institute for Rehabilitation, and Ms. Friedl at MetroHealth Hospital. For determining eligibility, the site physicians and site PIs (Drs. Plow, Forrest, Kirshblum, Pundik, Bryden and Cunningham) will review past medical history, history of present illness, family history when relevant, and review physical therapy and medical evaluation to make a final determination bout subject's eligibility.

All of patient's medical information, and PHI such as age, date of SCI, name, and address collected at the beginning of the study will be saved in a confidential manner at respective study sites. This private information will be protected and available only to the PI and authorized team members at each site. All identifiable information and health information will be stored separately from study data in a locked cabinet within a locked room. Only the study coordinator and the principal investigator at each site (Mr. O' Laughlin and Dr. Plow at the Cleveland Clinic, Ms. Martinez and Drs. Forrest and Kirshblum at Kessler Foundation/ Kessler Institute for Rehabilitation, Drs. Baker and Pundik at Cleveland VA Medical Center, and Ms. Friedl and Drs. Cunningham and Bryden at MetroHealth Hospital) will have access and will have the keys for the room and cabinet separate at each site. Keys will be stored away from plain sight in authorized individual's locked office cabinet. Any electronic files that contain identifiable information will be password-protected and only stored on computers with limited access as described below. The Cleveland Clinic, Cleveland VA Medical Center, the Kessler Foundation/ Kessler Institute for Rehabilitation, and MetroHealth Hospital provide networks that are secured for use by the authorized user only. All PHI will be stored on computers that are accessible only to the authorized team members on the study.

All identifiable information will remain at the parent study site (Cleveland Clinic, Kessler Foundation/ Kessler Institute for Rehabilitation, Cleveland VA Medical Center, and MetroHealth Hospital) and only de-identified information will be shared between sites (see special precautions later). Per guidelines of the Congressionally Directed Medical Research Programs (CDMRP), CDMRP-funded studies should make their 'final research data' as freely and widely available as possible. To meet this specification yet safeguard the privacy of our patients, and protect confidential and proprietary data, and any intellectual property, we would share de-identified data (see Precautions later). Since subaward sites, MetroHealth and Kessler Foundation/ Kessler Institute for Rehabilitation, are both SCI Model System centers, we would request co-investigators at these institutions (Drs. Kilgore, Bryden, Forrest, Kirshblum, Yue) to enter the de-identified data describing the clinico-demographic characteristics, function, and level of independence in self-care etc., in the national database. This process will be facilitated because we use common data elements (CDEs). Sharing of de-identified data based on CDEs would allow all SCI Model Systems across the U.S. to have access to our raw (de-identified) values and the change to compare values from our patients with the values from their patients and participants. In the informed consent process, patients will be made aware of the sharing of de-identified data via the SCI Model Systems database.

Accurate and complete study records from both sites will be maintained and made available only to representatives of the respective institutional review boards (IRBs), the U. S. Food and Drug Administration (FDA), the Department of Health and Human Services and representatives of the U.S. Army Medical Research and Materiel Command (USAMRMC). In unusual situations, all study sites will comply with legal requirements that mandate disclosure of identifiable information. The IRB-approved research consent document includes Health Information Portability and Accountability Act (HIPAA) authorization elements in the privacy and confidentiality section, where it will be explained that data from patients can be shared with federal authorities (listed above) and representatives of USAMRMC as stated above and that de-identified data can be shared with researchers at the Cleveland Clinic, Kessler Foundation/Kessler Institute for Rehabilitation, and Cleveland VA Medical Center, and SCI Model Systems database via Metrohealth and Kessler Foundation/Kessler Institute for Rehabilitation. Informed consent process will also explain that subjects have the right to withdraw their

authorization at any time and if they choose not to sign the consent form, they are choosing not to participate in the research study.

Dr. Kilgore and Dr. Bryden from MetroHealth Rehabilitation institute in Cleveland will be informing their patients with SCI of our study at the Cleveland Clinic. To maintain confidentiality of patients from MetroHealth, Dr. Kilgore and Ms. Bryden will not release any PHI about their patients. They will simply inform their patients of the study at the Cleveland Clinic site (see letters from Kilgore and Bryden). It would be at the patient's discretion as to whether or not they want to follow up with study staff at lead site or local site in Cleveland (Cleveland Clinic or Cleveland VA Medical Center). In the event that interested participants contact the study staff, it would be their discretion to release information to participate in the study. Therefore, even though co-investigators at other institutions would initiate referrals, privacy and confidentiality will be ensured.

Each site will comply with the same management plan for PHI. Whether a participant was enrolled or could not screen in into the study, we would ensure that their PHI is stored and accessed securely. Identifiable and protected health data of enrollees will be saved for 6 additional years after expiration of study authorization based on Code of Federal Regulations (45 CFR 164.530(j)(2).

9.4 Data Analysis Plan

For aim 1, measures of function, strength/muscle power, dexterity, sensation, prehension, perception of independence in self-care, and quality of life will be collected, while for aim 2, metrics characterizing neurophysiology will be acquired and for aim 3, vital measurements will be noted daily.

Functional metrics adopted here are part of the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDEs), developed through the collaboration of the International Spinal Cord Society, the AIS, and the NINDS. The functional metrics span across all domains of the World Health Organization's (WHO's) International Classification of Function (ICF) model, including body function and structure, activity limitations, and participation restrictions. Metrics include Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP), comprising the Upper Extremity Motor Score (UEMS) for strength, Nine-hole peg test (NHPT) for dexterity and sensation and prehension; Wolf Motor Function Test (WMFT) for measurement of functional abilities; Spinal Cord Independence Measure (SCIM) for evaluation of patient's ability to perform self-care; Canadian Occupational Performance Measure (COPM) to identify the patient's perceived level of daily participation in functional activities (e.g. cooking, cleaning, and hobbies). Each set of tests gives a different perspective of disability and testing all will allow us to get a full picture of patient function and quality of life before and after therapy. All measurements for aim 1 will take 120-150 min to complete. We will determine whether patients receiving tDCS in conjunction with rehabilitation experience greater recovery of function and independence than patients who receive rehabilitation alone (aim 1).

In aim 2, we will study the patient's neurophysiology, which will include the study of excitability of output pathways to a weaker muscle and a stronger muscle, and the cortical representations of these muscles. These measures of neurophysiology will be acquired using TMS and Hoffman or H-reflex. Neurophysiological tests will take 150-180 min to complete, which includes time allotted for breaks. We will test whether patients receiving tDCS in conjunction with rehabilitation experience greater gains in excitability of substrates devoted

to the weak muscle and larger decreases in the excitability of the substrates devoted to the stronger muscle than patients receiving rehabilitation alone (aim 2).

For aim 3, we will compare effects of interventions on patient's vital measurements, attrition, experience of adverse events (AEs) like tingling, itching, burning underneath the electrodes and likelihood of correctly guessing the group allocation. We anticipate that patients receiving tDCS in conjunction with rehabilitation will show no greater adverse effects or attrition than those receiving rehabilitation alone.

9.5 Sharing Study Results

Since neurophysiology tests are not diagnostic, no clinical report will be generated. But data from screening and functional outcomes, such as that collected by SCI physicians (Dr. Bethoux at the Cleveland Clinic; Dr. Richmond at the Cleveland VA Medical Center; Dr. Kirshblum at Kessler Foundation; Dr. Wilson at MetroHealth Hospital) and physical therapists to determine eligibility is used in clinical diagnosis as well. This includes the International Standards for Neurological Classification of SCI (ISNCSCI) for confirmation of diagnosis and American Spinal Injury Association (AIS) for rating the completeness of injury (A, B, C, and D) and zones of partial preservation below the level of injury. Physicians and therapists also record strength or muscle power using UEMS, and spasticity using MAS. Complaints of neuropathic pain and evidence of autonomic symptoms are noted as well. Diagnosis of associated TBI is made based on original radiographs and clinical records, and history and physical examination. Further, in line with aim 3, vitals and symptoms such as fatigue, restlessness, trouble concentrating, pain, etc. will be recorded. If an incidental finding is observed during the screening, i.e., a result that was not evident from original medical record review, or if a patient consistently demonstrates abnormal values during safety testing, then the study physicians, Dr. Bethoux at the Cleveland Clinic, Dr. Richmond at the Cleveland VA Medical Center, Dr. Kirshblum at Kessler Foundation/Kessler Institute, and Dr. Wilson at MetroHealth Hospital will notify the patient's primary care provider, referring physician or SCI physician to share findings. Regarding healthy controls as well, a similar protocol will be followed.

9.6 Special Precautions

Special precautions taken during laboratory evaluations to ensure patient safety: TMS carries a rare risk of seizures. Plus, patients with cervical SCI could experience autonomic dysfunction. To manage any AE therefore we will perform all procedures under the supervision of the Clinical Research Unit (CRU). CRU resources will be indispensable for patient safety and comfort in the current study. CRU comprises of a core group of clinical research administrators who help assure the most efficient and effective ways for researchers and clinical trials participants to interact. CRU coordinates and provides a culturally sensitive and welcoming clinical environment for volunteer research participants, inpatient and outpatient facilities such as examination rooms, specialized procedure rooms, core laboratories, services such as metabolic meal preparation, research dietician consultation, human exercise performance measurement and highly trained personnel to carry out research protocols in the hospital and in outpatient medical centers. Experienced research nurses staff both inpatient and outpatient areas. The research nursing staff is highly trained in initiating and maintaining time-sensitive procedures. Resources also include on-site crash code cart for immediate medical attention and drugs specific to potential risks associated with different protocols. The arrangement of CRU support will be similar to that used in Dr. Plow's current clinical trials where any TMS-based studies are conducted with CRU supervision by trained research nurses and on-call physicians to manage risks of seizures, and headaches. In consultation with

SCI physicians and CRU, a seizure protocol is put in place to ensure that in case of an AE, medical attention is prompt, such as crash cart availability and on-site medications and patient is stabilized without difficulty.

Safeguards and procedures are in place to ensure GCP are followed. Specifically, on-call CRU nursing staff and trained study staff will continually monitor patient safety and health during each site visit. Every 1 hour or whenever it becomes necessary, vital monitoring will be performed by CRU nursing staff, where values including blood pressure, heart rate, oxygen saturation and respiratory rate will be collected. In case vital measurements are significantly abnormal or a serious AE occurs, hospital-wide medical emergency response team will be paged; on-call physician (Dr. Bethoux at the Cleveland Clinic; Dr. Richmond at the Cleveland VA Medical Center; Dr. Kirshblum at Kessler Foundation and Kessler Institute for Rehabilitation; Dr. Wilson at MetroHealth Hospital) will be contacted and on-call CRU nurses will be reached as well. Depending on the type of emergency, SCI physicians and emergency response team will determine the next course of action. In addition, study staff will always record minor but noticeable changes in patient's state and vitals. All staff will be required to have completed the basic life support training before conducting procedures on the study.

To date, no AEs have occurred during the duration of our current SCI pilot study. This is likely since we use fairly strict inclusion and exclusion criteria. However, should an AE occur that could have been prevented, clinical coordinators, under the direction of PI/Co-I's, will update the patient screening process to identify what makes a patient susceptible to such an event. In addition, all patients currently participating in the clinical trial would be informed of the event and any subsequent changes to the consent form through a re-consenting process.

Special precautions taken to ensure confidentiality during data compilation and data sharing across sites: Raw data of neurophysiology and functional metrics shared between Cleveland Clinic, Cleveland VA Medical Center Kessler Foundation/Kessler Institute for Rehabilitation and MetroHealth Hospital will be de-identified and placed on locked drives and will not affect patient confidentiality. Since only a copy of de-identified data will be transported between sites, original data will still be available at each site in case the copy is damaged or destroyed in transport. Still, to ensure that data is completely de-identified and that privacy rules are being followed, we will take additional precautions.

Data will be collected without the use of the any of the 18 protected health identifiers, which could be used to identify the individual or the individual's relatives, employers, or household members. De-identified data will not have names, geographic divisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes; elements of dates (except year) for dates directly related to an Individual, including birth date, admission date, discharge date, date of death, and all ages over 89 and all elements of dates (including year) indicative of such age; telephone numbers; fax numbers; electronic mail addresses; social security numbers; medical record numbers; health plan beneficiary numbers; account numbers; certificate/license numbers; vehicle identifiers and serial numbers, including license plate numbers; device identifiers and serial numbers; web universal resource locators (URLs); internet protocol (IP) address numbers; biometric identifiers, including finger and voice prints; full face photographic images and any comparable images; and any other unique identifying number, characteristic, or code, except as otherwise permitted.

Informed consent process will seek approval from patient for sharing of de-identified study-related data with researchers at the other sites- Cleveland Clinic, Kessler Foundation/Kessler Institute for Rehabilitation, Cleveland VA Medical Center, and MetroHealth Hospital. Since per guidelines of CDMRP, CDMRP-funded studies should make their 'final research data' as freely and widely available as possible, while safeguarding privacy of patients, and protecting confidential and proprietary data, and any intellectual property, we would share raw data that is completely de-identified. Raw data of neurophysiology and functional metrics, which are completely de-identified, and ascribed dummy study identification codes will be uploaded to the SCI Model Systems database through two of our collaborating sites that are also leading model systems centers, including Kessler Foundation/Kessler Institute for Rehabilitation and Metrohealth Rehabilitation Institute Cleveland.

10.STUDY ADMINISTRATION

10.1 Data Safety Monitoring Board (DSMB)

This study will be performed in accordance with the Charter of the Data and Safety Monitoring Board (DSMB) provided below. The members of the Board are

- Paul T. Scheatzle, DO, MS, Fellow of the American Academy of Physical Medicine and Rehabilitation (FAAPMR) (Medical Monitor), Chair

  Bailey Rehabilitation Services

- Steven W. Brose, DO

  Syracuse VA Medical Center; Spinal Cord Injury and Disorders Center

- Doug Gunzler PhD (Biostatistician)

  Case Western Reserve University; Center for Health Care Research and Policy

- Denise Peters, PT, PhD (Research Monitor)

  University of Vermont

- Mr. Christopher Wynn (Consumer Advocate)

  Buckeye Wellness Center

Dr. Steven Brose is Chief of Spinal Cord Injury at the Syracuse VA Medical Center in New York State. He has extensive experience in spinal cord injury in both clinical and research settings. Dr. Paul Scheatzle is a Physiatrist at the Edwin Shaw Rehabilitation Institute (Cuyahoga Falls, Ohio). He has over 21 years specializing in physical medicine and rehabilitation. Dr. Denise Peters of the University of Vermont's College of Nursing and Health Sciences is a physical therapist and rehabilitation scientists with research expertise in translating mechanistic research to evidence-based clinical application in the field of neurologic rehabilitation specifically spinal cord injury. Mr. Wynn is a military veteran, and owner of Buckeye Wellness Center (Valley View, Ohio), which specializes in training those with spinal cord injury in exercise programs. As part of the DSMB, Mr. Wynn will serve as the consumer advocate.

The DSMB will be responsible for reviewing the draft DSMB charter, safety and efficacy of the phase I/II clinical trial, and reviewing any adverse events occurring during this study. The Board will have the authority to make a final ruling on contested site-reported events as necessary and appropriate.

The Charter of the Data and Safety Monitoring Board is attached (with names of the committee members redacted, per instructions).

10.1a DSMB Responsibilities

The DSMB will review the draft DSMB charter and make recommendations for any changes.

The DSMB will monitor the safety of the trial via a report provided by Douglas D. Gunzler, PhD, Case Western Reserve University (Cleveland, Ohio).

The initial review of the data by the full DSMB will take place after the first 13 patients have completed the study. Thereafter, the DSMB will meet after every 13th patient has completed the study, or at least once a year, to examine the safety of the trial in accordance with Aim 3 of the study and integrity of data collecting in terms of efficacy in Aim 1. These assessments will include, at a minimum, a review of all adverse events, deaths, or deviations from the study protocol and results of functional outcomes and metrics.

The DSMB will make recommendations to the Trial Operations Committee regarding the modification or continuation/discontinuation of the trial.

DSMB member Dr. Denise Peters is the Research Monitor of this Project. As described in the Department of Defense Instruction 3216.02, Dr. Peters is responsible in overseeing the safety of the research subjects and report observations/findings to the IRB. She will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. She may discuss the research protocol with investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official, other DSMB members, and the HRPO.

10.1b DSMB Meetings

The first meeting of the DSMB will be an organizational meeting. This meeting is intended to formally establish the DSMB and to thoroughly acquaint the DSMB with the protocol and the interim analysis plan. It also affords the DSMB an opportunity to recommend final revisions of the interim analysis plan, the DSMB protocol, mock tables, and the plan for communication between the DSMB and the Sponsor/Investigator.

1. The initial review of the data by the full DSMB will take place after the first 13 patients have completed the study. Thereafter, the DSMB will meet after every 13th patient has completed the study, or at least once a year.
2. The DSMB will determine if additional reviews of the data are needed. If necessary, the DSMB can request more frequent reports.
3. The confidential DSMB reports will be hand delivered to the members 5 days before the scheduled meeting.

4. Statisticians will send the DSMB quarterly summaries of adverse events, endpoints, and device data. Whenever the DSMB thinks it is necessary, a full DSMB conference call will be held.

The DSMB meeting will consist of three parts:

1. *Open Discussion*: The first part of the meeting will be attended by the DSMB members, the statistician (Dr. Xiaofeng Wang), and the Trial Operations Committee. Its purpose is to discuss the conduct of the trial, study status, and issues related to data quality and interpretation.
2. *Presentation of the Results*: The DSMB members and the statistician will attend the second part of the meeting only. During this part of the meeting, the statistician will present the results of the statistical analysis of the study to the DSMB members.
3. *Closed Discussion*: The third part of the meeting will be attended by DSMB members only. During this part, the board will discuss the results and make any decisions regarding the conduct of the trial. Based on its review, the DSMB may, if warranted, recommend one of the following actions to the sponsors.
    a. *Continue* the study according to the protocol and any existing amendments.
    b. *Continue* the study, but *modify the study protocol.* Modifications may include, but are not limited to, changes in the inclusion/exclusion criteria, frequency of safety monitoring, and alterations in study procedures and follow-up period for purposes of safety as defined in the protocol.
    c. *Discontinue* the study, with provisions for orderly discontinuation in accordance with good clinical practice.
4. Confidential minutes will be recorded. They will be stored in a secured location by the statistician.
5. As soon as possible, but within 3 days following each of its meetings, the DSMB will prepare a written report for the Trial Operations Committee outlining any serious safety concerns and explaining their recommendations.

10.1c Making Recommendations

The DSMB may recommend one of the following actions to the Trial Operations Committee (fig 4):

1. Stop the Study
2. Continue the Study without changes
3. Change the Protocol

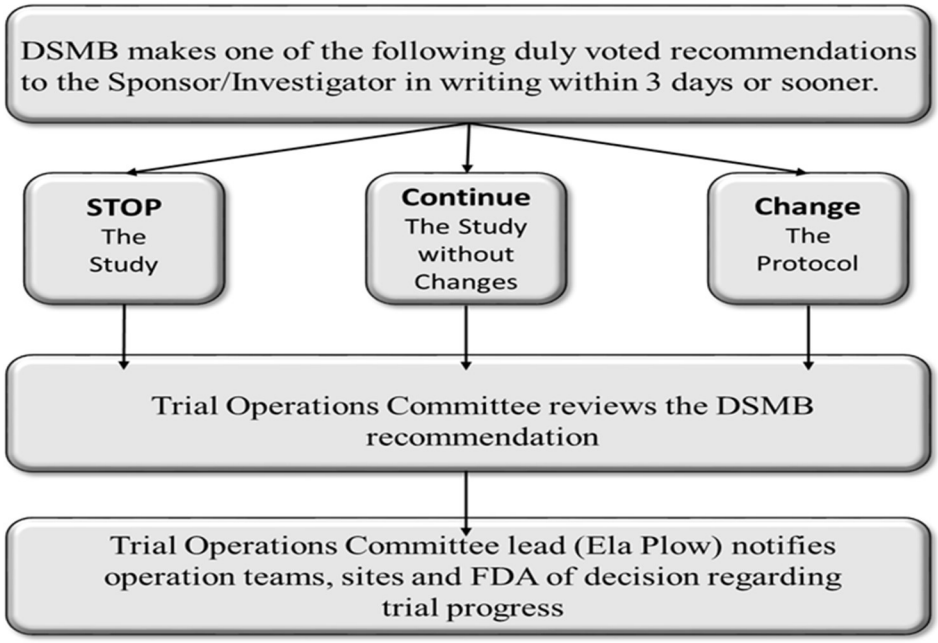

Fig. 4

10.1d DSMB Decision Guidelines for stopping the trial

Upon review of the data while the trial is in progress, the DSMB will make decisions regarding the continuation of the trial. The final decision to stop the trial is left to the recommendation of the DSMB.

10.1e Elements of the DSMB Reports

Dichotomous and categorical data will be reported as total numbers and percentages. Continuous data will be reported as means, medians, and standard deviations.

Reports should have page numbers and sections need to have explanatory tabs.

If objectives are different for subsequent DSMB meetings, the meeting minutes should reflect the report(s) needed for each meeting.

Elements of the DSMB Report:

1. Patients enrolled
2. Protocol deviations
3. Selected clinical risk factors
4. Demographic/baseline factors to include gender, race, and age
5. Deaths (patient listing of the event to indicate study-related vs. not study-related)
6. Serious and/or severe adverse events and unanticipated adverse device effects on subjects

7. Narrative reports of serious adverse events
8. Narrative reports of subject outcomes

The DSMB report will include the total number of patients whose data were derived from final Case Report Forms (CRFs).

11.RISKS/BENEFITS

Foreseeable Risks: There are several risks involved with the proposed study procedures that are either related to techniques/devices proposed for the present study or are unrelated to study procedures but represent risks intrinsic to the nature of the study population – those with tetraplegia.

11.1 Risks associated with TMS

Transcranial magnetic stimulation (TMS) has been used in a growing number of laboratories worldwide since 1984, and safety guidelines have been developed. In the present study, the investigators will use all recommended safety precautions for TMS. Although unlikely, given the low levels of stimulation applied in the present study, the following side effects are still possible:

- Headache: Subjects may have a headache following TMS. This is believed to be due to muscle tension. In the case of headache, subjects will be offered acetaminophen or aspirin, which in all prior cases of headaches induced by TMS have promptly resolved the discomfort. The risk of headache is estimated to be approximately 10%-25%.
- Hearing: TMS produces a loud clicking sound when a current is passed through the stimulation coil. This loud clicking can result in ringing in the ear and temporary shifts in the subject's ability to determine the pitch and loudness of sounds, if no protection is used. To prevent this possible side-effect, we will ask subjects to wear earplugs that block the noise of the TMS. Hearing damage is possible; one person is known to have suffered permanent hearing damage when the hearing protection fell out of the ear. Animal and human studies have shown that earplugs or headphones can effectively prevent the risk of hearing disturbance due to TMS.

There are also several rare side effects of TMS:

- Seizure: Subjects may have a seizure induced by TMS. If a seizure were to occur, it would occur during the TMS application itself, not after. If the subjects are currently taking a prescription medication that has the potential to lower the seizure threshold, they may be at increased risk for seizure from the procedures in this study. It will be made clear to them that they must maintain their current medications at the prescribed dose for the entirety of their involvement in this study. Seizures are a very rare complication. First, the TMS levels that we propose to use have never been reported to induce a seizure. Second, during the TMS session, subjects will undergo continuous monitoring of EMG activity to allow investigators to detect the earliest warning signs of a seizure and be able to prevent it. Nevertheless, a seizure could occur. For this reason, TMS will be applied by investigators properly trained in the prompt recognition and treatment of a seizure and certified in basic life support. Clinical Research Unit nursing support, physicians, and resources, such as "crash cart" medications related to seizure protocol, will be available. Should a seizure occur, subjects will receive prompt treatment by a physician. Experiencing a seizure induced by TMS does not mean that subjects will have another seizure again; it does not make the subject an epileptic person and will not mean that subjects will have to take medications to prevent seizures in the future. A letter approved by the FDA documenting these facts will be offered to any subject who experiences a seizure induced by TMS. Nevertheless, seizure occurrence with single-pulse

TMS is rare. Only two persons have had seizures induced by the approach of TMS we are using (single-stimulus/-pulse TMS) among the many thousands of subjects who have undergone TMS worldwide. Furthermore, the investigators will use precautions to further reduce the risk.

- Memory or attention may be affected for a short period of time (a few minutes) after receiving TMS. The low TMS levels used in this study have never been shown to cause such problems.
- There may be unforeseen risks to an unborn child associated with undergoing TMS. To address this risk, women subjects will be excluded from the study if they are found to be pregnant during our prior testing procedures.
- Finally, even though TMS has been used in many laboratories worldwide since 1984, there could be some unforeseen complications. There may be unforeseen risks to an unborn child associated with undergoing TMS. To address this risk, subjects will be excluded from the study if they are found pregnant during our testing procedures.

11.2 Risks associated with tDCS

Although many researchers have studied the safety of transcranial direct current stimulation (tDCS) and determined that it is a painless stimulating technique with almost no harmful effects, there are several minor adverse effects that need to be reported. These effects include:

- Temporary itchiness and/or redness of the skin in the area of stimulation. The reddening is transient for levels of stimulation proposed in this protocol. However, skin will be inspected regularly at the site of stimulation to ensure redness is relieved.
- Transient and mild headache, tingling, and a burning sensation in the area of stimulation. However, these effects have been reported while delivering higher doses than what will be used in the proposed study.
- Application of tDCS might result in temporary cognitive and motor side effects such as dizziness, disorientation, or confusion. These effects are transient, and the subject will be constantly supervised by study staff.

11.3 Risks associated in the SCI patient population

The patient population we propose to study, those with tetraplegia, is typically more functionally limited, since the injury affects all limbs and the trunk. Further, in comparison to those with paraplegia, many patients with tetraplegia have reported severe difficulties with neuropathic pain, sensation, walking, bladder and bowel function, trunk stability, sexual function, and arm/hand function. They also typically present with more serious co-morbidities, especially autonomic emergencies, spasticity, and depression. Therefore, even though their co-morbidities may be unrelated to study procedures, patients can still experience the following:

- *Autonomic dysreflexia:* This syndrome occurs in individuals with spinal cord lesions above the T6 level. Since the proposed study plans to enroll patients with levels of injury between C1 and C8, patients may be at risk for autonomic dysreflexia. The syndrome is caused by overstimulation of the involuntary nervous system, which is usually a result of improper emptying of the bowels or bladder or a urinary tract infection. Study staff is aware of the symptoms of autonomic dysreflexia (severe hypertension, headaches, sweating, flushing of skin, and slow heart rate). If a patient develops the syndrome during a study session, the patient will immediately inform the responsible treating physician. Clinical Research Unit nurses will be on-site

during all sessions and will help identify signs early on. They will help initiate preventive measures, such as ensuring catheter bags are not full or there is no obstruction to catheter tubing. If an event occurs, study staff will initiate the emergency code for paging the emergency response team; the on-call physician will be paged, and nursing staff will implement the medical orders. With such precautionary measures, no autonomic emergencies have occurred in Dr. Plow's pilot clinical trial in patients with tetraplegia.

- *Exacerbated spasticity:* Some SCI patients experience spasticity, which is described as involuntary stiffness of the muscles. Depending on the severity, spasticity could affect the patient's comfort level as well as ability to perform tasks during the rehabilitation phase of the study. During the intervention, breaks will be provided to minimize fatigue and allow passive movements and stretching. Patients will be asked to maintain their dose of anti-spasticity medications.
- *Neuropathic pain:* Patients with SCI could have damaged nerve fibers, which transmit incorrect signals and cause pain. This neuropathic pain could affect the patient's comfort level as well as ability to perform tasks during the intervention phase of the study. The level of neuropathic pain will be taken into consideration when designing the specific intervention for a patient to minimize any exacerbation of the pain.

11.4 Benefits

Subjects will be receiving rehabilitation in the study, however, this will not guarantee benefit from their participation in the study.

12.INFORMED CONSENT MATERIALS

Informed Consent will be obtained from each study participant. The investigator and/or study coordinator at each respective site will approach the potential subject, verbally explain the study, and provide an IRB and HRPO approved written informed consent document for his/her review and signature. The site lead PI and coordinator will be available to answer all questions the subject may have pertaining to the nature of the study or any of the study procedures. Subjects will not be allowed to participate in any study procedures until informed consent is provided.

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