PROTOCOL TITLE: *Metaplasticity in the human motor cortex: validation of an experimental design and comparison of motor outcome measure sensitivity to change*

INSTRUCTIONS:

- *Use "TEMPLATE PROTOCOL (HRP-503)" to prepare a document with the information from following sections.*
- *Depending on the nature of what you are doing, some sections may not be applicable to your research. If so mark as "NA" and briefly explain why it doesn't apply. For example, research involving a retrospective chart review may have many sections with NA.*
- *If there is another protocol document (e.g., from a study sponsor), please include that protocol document with your submission in addition to this form. If content requested in this protocol template is already addressed in the other protocol document, please indicate the location by page and paragraph number rather than repeating the information here.*
- *If this research is HHS-supported (e.g., NIH funded) and UNM HSC is the prime awardee or serving as the IRB of record for the prime awardee, include a copy of the grant application and sample consent (if applicable).*
- *All checklists referenced in this protocol can be found in Click under the "IRB" tab, in the "IRB Library".*
- *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*
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PROTOCOL TITLE:

Metaplasticity in the human motor cortex: validation of an experimental design and comparison of motor outcome measure sensitivity to change

PRINCIPAL INVESTIGATOR:

Sarah Pirio Richardson, MD
Neurology

Davin Quinn, MD
Psychiatry

VERSION NUMBER:

V2

DATE:

12/16/2016

REGULATORY FRAMEWORK:

Please indicate all that apply:

☐	DOD (Department of Defense)
☐	DOE (Department of Energy)
☐	DOJ (Department of Justice)
☐	ED (Department of Education)
☐	EPA (Environmental Protection Agency)
☐	FDA (Food and Drug Administration)
☐	HHS (Department of Health and Human Services)
☐	VA
☐	Other:

Is this a clinical trial under ICH-GCP E6? ☒ Yes ☐ No

If yes, please confirm that the research team is familiar with and agrees to comply with the investigator requirements cited in ICH-GCP E6. ☒ Yes ☐ No

ICH-GCP E6 can be accessed by copying and pasting this URL into your browser: http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf

Table of Contents

1. Objectives

1.1. The overall objective is to validate the methodology of a metaplasticity experimental design by assessing change in motor excitability after administration of priming transcranial direct current stimulation (tDCS) followed by repetitive transcranial magnetic stimulation (rTMS) in healthy human participants. Our primary objective is to compare pre- and post-measures of cortical excitability before priming tDCS (anodal, cathodal or sham) [M1], directly after priming tDCS [M2], directly after inhibitory rTMS [M3], and 10 minutes after inhibitory rTMS [M4]. Our secondary objective is to evaluate the sensitivity of motor excitability outcome measures response to the noninvasive neurostimulation (e.g. rTMS and tDCS). Our future direction is to apply this validated protocol in patient populations to better understand how disease states affect metaplasticity.

1.2. ***Aim 1:*** *To compare pre- and post- measures of cortical excitability after inhibitory and excitatory priming of the motor cortex. Hypothesis 1: We expect priming tDCS to affect the response to rTMS, namely we expect "inhibitory" cathodal tDCS to cause a reversal of the normal inhibitory effect of 1Hz rTMS. Hypothesis 2: We expect "excitatory" anodal tDCS to have no effect on the normal inhibitory effect of 1Hz rTMS. Hypothesis 3: We expect sham tDCS to have no effect on the normal inhibitory effect of 1Hz rTMS.*

Exploratory Aim 2: *To evaluate the sensitivity of motor outcome measures to changes in cortical plasticity. Hypothesis 1: We expect different measures of motor cortex excitability to be more sensitive than others at detecting changes in cortical excitability. We will be comparing in an exploratory but systematic fashion various measures of motor cortex excitability (e.g. peak-to-peak amplitude change in motor evoked potential (MEP), the integrated area of the MEP (root mean square), the cortical silent period (CSP)), and behavioral measures (reaction time).*

2. Background

2.1. rTMS and tDCS are relatively new modalities that have shown promise in the evaluation and treatment in a variety of neurologic and psychiatric disorders as well as understanding normal brain processes in the healthy human brain. One specific area of interest has been the concept of metaplasticity in the motor cortex in healthy brains and how this is modified in the disease state. Metaplasticity refers to changes in synaptic efficacy such as long-term potentiation (LTP) and long-term depression (LTD), which can be influenced by prior neuronal activity. In humans, we can study these LTP-like and LTD-like changes using non-invasive neurostimulation (e.g. tDCS and rTMS).

2.2. Previous studies (Siebner et al. 2004) have shown that preconditioning with anodal ("excitatory") tDCS followed by inhibitory rTMS led to a period in which corticospinal excitability was reduced below baseline. Conversely, preconditioning with cathodal tDCS followed by 1Hz rTMS caused a resulting

period of corticospinal excitability that was increased above baseline. This will be a proof of principle trial to validate the methodology of this protocol.

2.3. rTMS is a relatively new therapeutic modality that shows great promise in the treatment and evaluation of a variety of conditions and is already FDA-approved for the treatment of depression. However, various target stimulation parameters and protocols make comparison across research groups difficult, leading to a knowledge gap. Validating a systematic methodological approach in healthy people will allow comparison to previous work as well as establishing a baseline for moving forward to compare metaplasticity in brain disease states.

3. Study Design

3.1. This will be a randomized, sham-controlled, double blinded crossover trial in a healthy population.

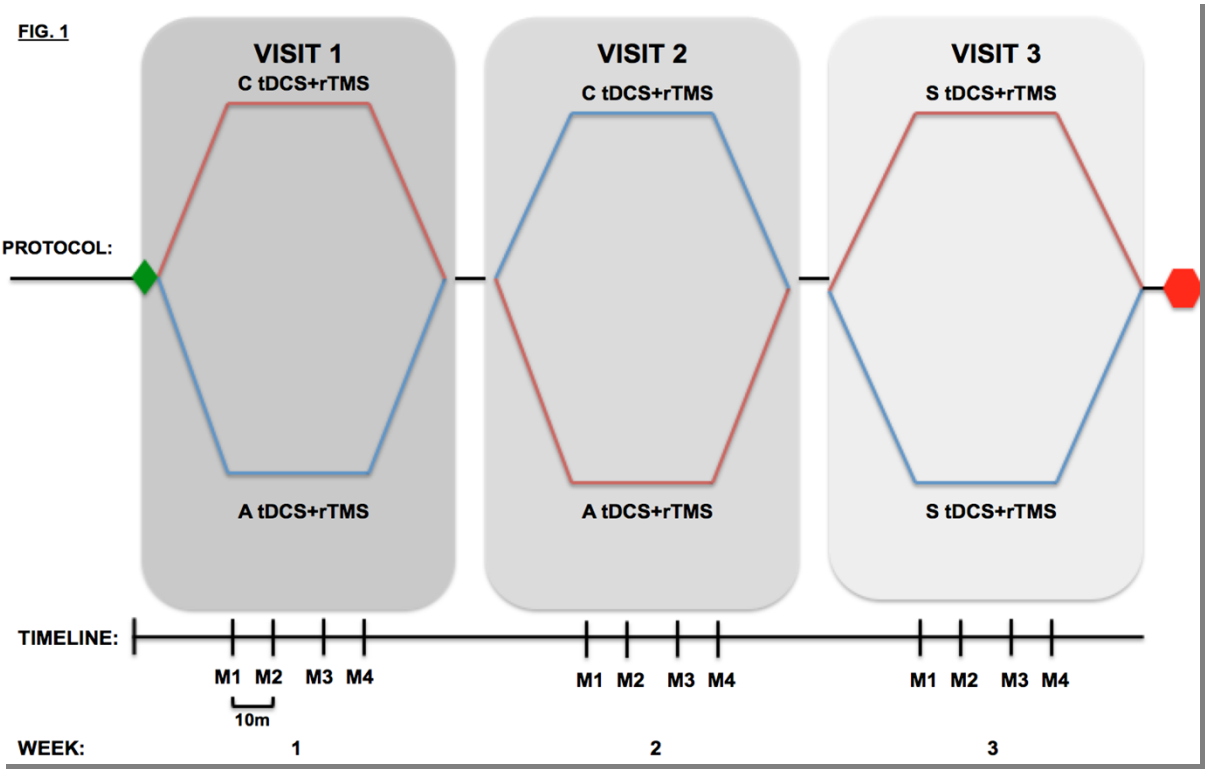

Figure 1: Subjects will enter the randomization at green diamond. Example shown for a subject following the red line through 3 interventions and another example shown in the blue line receiving a different order of interventions. They will be randomized to a three-visit crossover with a week separation between each visit. There will be four measures taken each visit (M1-M4), which will be approximately 10 minutes apart. Measures taken at each time point include: physiological measures (e.g. MEP), behavioral outcomes (e.g. reaction time) and exploratory outcomes. Study is completed at the end of visit 3 (red octagon). C tDCS=cathodal tDCS; A tDCS=anodal tDCS.

3.2. Participants will be blinded to treatment group. A team investigator, off-line, will conduct the raw data analysis (e.g. MEP amplitude and CSP) and will be different than the investigator applying the noninvasive neurostimulation to the

treatment group. This additional blinding of the data analysis will help to provide another protection against bias.

4. Inclusion and Exclusion Criteria

4.1. Individuals will be screened for eligibility by a study team member. The study team member will ask the potential participant a series of questions to determine whether or not they meet the inclusion/exclusion criteria.

4.2. <u>Inclusion Criteria:</u>

a) Participant must be at least 18 years of age (all genders, races, and ethnicities)

b) Participant must have no current psychiatric or neurologic issues

c) Participant must not have any conditions listed in the exclusion criteria

d) Participant must be fluent in English

<u>Exclusion Criteria:</u>

a) History of major psychiatric illness

b) Actively using a neuropsychoactive medication

c) Legal or mental incompetency

d) Substance use disorder, abuse or dependence, with active use within the last 3 months

e) Significant medical or neurological illness

f) Prior neurosurgical procedure

g) History of seizure

h) History of ECT or TMS treatment within the past three months

i) Presence of a pacemaker, implanted medical pump or device, metal plate, or metal object in skull or eye (including shunts, dental implants, facial tattoos with metallic ink)

j) Pregnant women

4.3. This study will not include any participants from any special populations (adults unable to consent, children, pregnant women, or prisoners).

4.4. This study will exclude pregnant women and children (due to safety and potential risk), prisoners and those who cannot competently provide their own consent (due to these groups being special populations) and will also exclude those who do not fluently speak or understand English (as our consent will be in English and study team members are fluent in English).

5. Number of Subjects

5.1. This is not a multisite study and will only recruit subjects at this site.

5.2. We will aim to recruit 16 subjects for this study.

5.3. Sixteen subjects will be enrolled for this study according to the MANOVA model (anodal, cathodal, and sham) and a specified number of variables (time points—M1-M4) at the significance level of $\alpha=0.05$ and 80% power to correspond to the very large effect size. We have based the calculation on the very large effect size as seen in Quartarone et al., 2005. The desired sample size was found to be 16 patients per treatment arm. We will fulfill this sample size requirement with a crossover design as all 16 subjects will participate in each treatment arm. We would request a recruitment ceiling of 20 subjects to account for subject dropout and if a subject were to meet exclusion criteria after signing the consent.

6. Study Timelines

6.1. Study subjects will participate in three visits total. Each visit will consist of a visit length of 1 to 1 ½ hours in duration. The visits will be approximately one week apart. There will be no scheduled follow-up after the third subject visit. We anticipate that it will take 8 months to enroll all subjects. We expect to complete enrollment of all subjects and completion of experiments in 1 year. We expect data analysis and publication to occur within 2 years of study commencement.

7. Study Endpoints

7.1. The primary endpoint will be change in motor evoked potential (MEP) amplitude over the first dorsal interosseous (FDI) muscle of the dominant (right) hand pre- and post-intervention (tDCS and rTMS—time points M1-M3) as well as 10 minutes post intervention (time point M4). The secondary endpoint will be the comparison in an exploratory but systematic fashion various measures of motor cortex excitability (e.g. peak-to-peak amplitude change in motor evoked potential (MEP), the integrated area of the MEP (root mean square), the cortical silent period (CSP)), and behavioral measures (reaction time).

7.2. We will collect data on the safety of rTMS in this patient population including expected side effects: headache (expected 17% with transient headache that responds to simple analgesic) and nonspecific feelings of discomfort. We will collect data on rare but serious adverse events such as seizures (reported at 1.4%). No seizures have been reported in the literature on rTMS in the dystonia population thus far (Lefaucheur et al., 2014).

8. Research Setting

8.1. The study visits will all take place in the Noninvasive Neurostimulation Lab located on the 2nd floor of the Clinical and Translational Science Center (CTSC).

8.2. Potential subjects will be recruited and identified through the healthy participant registry through the CTSC as well as fliers placed throughout the Health Sciences Center and Main Campus.

8.3. Research procedures will be performed in the Noninvasive Neurostimulation Lab located on the 2nd floor of the CTSC. Analysis will be performed between the offices of Dr. Pirio Richardson, Dr. Quinn, and the CTSC Biostatistics core.

8.4. N/A

8.5. N/A

9. Resources Available

9.1. PI: Dr. Sarah Pirio Richardson will be responsible for supervising and coordinating all aspects of the research. She is well prepared and qualified for this role. Her training includes a fellowship at the National Institute of Neurological Disorders and Stroke in the Human Motor Control Section with Dr. Mark Hallett, which provided her with experience and expertise to undertake clinical research with noninvasive neurostimulation. She has completed the NIH Clinic Center Research Curriculum Certificate with Commendation. Additionally, she has published multiple studies using rTMS in healthy subjects and various movement disorders. She is well prepared to conduct research in the population. Dr. Pirio Richardson recently completed a KL2 scholar position through the CTSC providing formal mentorship and training in clinical and translational research.

Co-PI: Dr. Davin Quinn is an Associate Professor in Psychiatry. As a junior PI in the UNM Center for Brain Recovery and Repair, Dr. Quinn's goal is to establish an independent NIH-funded research program in neurorehabilitative and neurostimulatory therapies for affective, behavioral, and cognitive sequelae of traumatic brain injury (TBI). The current proposal will study the administration of high-definition transcranial direct current stimulation and transcranial magnetic stimulation to temporarily modulate the homeostatic plasticity of the brain in healthy subjects, bringing together several of his academic interests in one scientific endeavor. Dr. Quinn has made the treatment of TBI the focus of his clinical work for the past several years, achieving board-certification in neuropsychiatry and behavioral neurology in 2012, and establishing a neuropsychiatry clinic in the UNM Clinical Neurosciences Center in 2013 to better serve the undertreated population of TBI patients in New Mexico. Dr. Quinn joined the UNM Electroconvulsive Therapy (ECT) Service in 2012 after becoming certified in ECT. He has published several articles on the efficacy and safety of various neurostimulation modalities.

Co-I: Dr. Andrew Archer is a third-year Psychiatry resident interested in pursuing an academic career and is interested in noninvasive neurostimulation. He has participated in several research studies within the Psychiatry department. He has completed the required trainings to be able to conduct clinical research responsibly.

Research Coordinator: Ms. Ashley Wegele is a research coordinator in the Department of Neurology (supervised by Dr. Pirio Richardson). She has completed all required training for clinical research and regulation. She will manage all regulatory correspondence with the IRB and the funding agency such

as progress reports and adverse event reporting. She will obtain subject consent and HIPAA authorization. She will schedule and facilitate all subject interactions, as well as collect and manage research data.

9.2. Drs. Pirio Richardson and Quinn will be responsible for any medical decision-making and ordering and evaluation of necessary diagnostics and therapeutics.

9.3. Other resources available

- *This study requires a small number of healthy participants. Given the registry maintained by the CTSC along with the number of healthy people who frequent the UNM campus and may see our flier, we believe it will be feasible to recruit our sample.*
- *Our study team will devote ample time to the all phases of this research project. Time necessary may fluctuate depending on how many participants are interested at a particular time. Our team comprises of several individuals with the training and expertise necessary to devote the time needed until the project is completed.*
- *Laboratory space and equipment: Dr. Pirio Richardson's, Noninvasive Neurostimulation Laboratory at UNM (476 nsf), is housed at the University of New Mexico Clinical and Translational Science Center (CTSC) on the second floor of the building. On this floor, a main reception area and front desk check-in for study appointments. The lab contains all equipment necessary to conduct noninvasive transcranial magnetic stimulation (TMS) studies. Both a Magstim 200^2 (plus the Bistim^2 unit) (Magstim Co., Whitland, Dyfed, UK) and a Magstim Rapid^2 (Magstim Co., Whitland, Dyfed, UK) are used in the laboratory. The coil inventory includes a Magstim double 70mm coil, Magstim custom double 35mm coils, and Magstim double 70mm cooled coil system and a Magstim double 70mm sham coil system (1st generation), (Magstim Co., Whitland, Dyfed, UK). For this project, a set of real vs. sham Magstim (2nd generation) air-cooled coils are requested to match the same set of coils in use at all other sites. The TMS units are connected to a commercial electromyography machine (Nicolet Viking) through a data acquisition device (Micro 1401, Cambridge Electronic Devices, Cambridge, UK). The data are collected and analyzed through Signal software (Cambridge Electronic Devices, Cambridge, UK). The lab is also equipped with custom hardware, including a flexible overhead coil holders and optional chin-rest and neck brace for stabilizing the subject's head during experiments and chair with arm and leg rests.*
- *A NeuroConn MR transcranial electrical stimulator belonging to the Clinical Core will be used. This is a CE-certified medical device for conducting non-invasive transcranial direct current stimulation (tDCS), alternating (tACS) or random noise (tRNS) current stimulation on subjects. Transcranial stimulation using weak electric currents over a period of several minutes is demonstrated to modify neuronal excitability and circuit function and can serve to promote brain recovery and repair.*

- *Although risk for seizure is minimal, in the event this occurs the PI (Dr. Pirio Richardson) will be on hand to administer immediate first aid and the hospital code team would be activated.*
- *All members of our small study team are involved in the development of this protocol. Upon approval, we will meet regularly to ensure that our research protocol is being appropriately implemented. Furthermore, there will be at least two members of the research team available for participant visits, ensuring accountability and safety procedures are being met.*
- *The signed CTSC resources attachment will be uploaded on the CTSC Submission page in Click.*

10. Prior Approvals

10.1. N/A

10.2. Attached to submission

10.3. N/A

10.4. N/A

11. Multi-Site Research

11.1. N/A

11.2. N/A

11.3. N/A

12. Study Procedures

12.1. Visit 1:After informed consent, subjects will be seated in a comfortable chair. Surface EMG leads will be applied to clean and prepped skin over the right hand over the first dorsal interosseous muscle (FDI). The motor hotspot for FDI will be identified with TMS on the contralateral hemisphere. Resting motor threshold and active motor threshold will be determined.

- ***M1*** *(pre-tDCS measurement): neurophysiological outcome assessment (MEP, CSP) and behavioral outcome (reaction time task)*
- ***Priming Intervention*** *10 min tDCS (cathodal, anodal or sham)*
- ***M2*** *(pre-tDCS measurement): neurophysiological outcome assessment (MEP, CSP) and behavioral outcome (reaction time task)*
- ***Inhibitory Intervention*** *15 min rTMS over the dominant primary motor cortex at 1Hz*
- ***M3*** *(post-rTMS measurement): neurophysiological outcome assessment (MEP, CSP) and behavioral outcome (reaction time task)*
- ***M4*** *(10 minutes post-rTMS measurement): neurophysiological outcome assessment (MEP, CSP) and behavioral outcome (reaction time task)*

Visit 2:

- ***M1*** *(pre-tDCS measurement): neurophysiological outcome assessment (MEP, CSP) and behavioral outcome (reaction time task)*
- ***Priming Intervention*** *10 min tDCS (cathodal, anodal or sham)*
- ***M2*** *(pre-tDCS measurement): neurophysiological outcome assessment (MEP, CSP) and behavioral outcome (reaction time task)*
- ***Inhibitory Intervention*** *15 min rTMS over the dominant primary motor cortex at 1Hz*
- ***M3*** *(post-rTMS measurement): neurophysiological outcome assessment (MEP, CSP) and behavioral outcome (reaction time task)*
- ***M4*** *(10 minutes post-rTMS measurement): neurophysiological outcome assessment (MEP, CSP) and behavioral outcome (reaction time task)*

Visit 3:

- ***M1*** *(pre-tDCS measurement): neurophysiological outcome assessment (MEP, CSP) and behavioral outcome (reaction time task)*
- ***Priming Intervention*** *10 min priming tDCS (cathodal, anodal or sham)*
- ***M2*** *(pre-tDCS measurement): neurophysiological outcome assessment (MEP, CSP) and behavioral outcome (reaction time task)*
- ***Inhibitory Intervention*** *15 min rTMS over the dominant primary motor cortex at 1Hz*
- ***M3*** *(post-rTMS measurement): neurophysiological outcome assessment (MEP, CSP) and behavioral outcome (reaction time task)*
- ***M4*** *(10 minutes post-rTMS measurement): neurophysiological outcome assessment (MEP, CSP) and behavioral outcome (reaction time task)*

13.Data Analysis

13.1. ***Aim 1:*** *To compare pre- and post- measures of cortical excitability after inhibitory and excitatory priming of the motor cortex. Hypothesis 1: We expect priming tDCS to affect the response to rTMS, namely we expect "inhibitory" cathodal tDCS to cause a reversal of the normal inhibitory effect of 1Hz rTMS. Hypothesis 2: We expect "excitatory" anodal tDCS to have no effect on the normal inhibitory effect of 1Hz rTMS. Hypothesis 3: We expect sham tDCS to have no effect on the normal inhibitory effect of 1Hz rTMS. We will use a MANOVA model (anodal, cathodal, and sham) and a specified number of*

variables (time points—M1-M4). MANOVA assumes normality of the residuals and equality of variance across groups. In the case of violation of these assumptions, we will explore data transformations, including logarithmic, power, and inverse-normal transformations, to identify an analytic scale under which modeling assumptions are met. Should transformations not be adequate, we will employ non-parametric methods instead.

Exploratory Aim 2: *To evaluate the sensitivity of motor outcome measures to changes in cortical plasticity. Hypothesis 1: We expect different measures of motor cortex excitability to be more sensitive than others at detecting changes in cortical excitability. We will be comparing in an exploratory but systematic fashion various measures of motor cortex excitability (e.g. peak-to-peak amplitude change in motor evoked potential (MEP) and the integrated area of the MEP (root mean square)) with the cortical silent period (CSP) and behavioral measures (reaction time). We will perform both a linear regression as well as a Principal Components Analysis (PCA) to identify which cortical excitability factors are most sensitive to change due to noninvasive neurostimulation.*

13.2. Power analysis: Sixteen subjects will be enrolled for this study according to the MANOVA model (anodal, cathodal, and sham) and a specified number of variables (time points—M1-M4) at the significance level of $\alpha=0.05$ and 80% power to correspond to the very large effect size. We have based the calculation on the very large effect size as seen in Quartarone et al., 2005. The desired sample size was found to be 16 patients per treatment arm. We will fulfill this sample size requirement through a crossover trial as all 16 subjects will participate in each treatment arm. We would request a recruitment ceiling of 20 subjects to account for subject dropout and if a subject were to meet exclusion criteria after signing the consent.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects

14.1. The PIs will consist of the medical monitoring team for this study due to its minimal risk status.

14.2. We will collect data on the safety of rTMS including expected side effects: headache (expected 17% with transient headache that responds to simple analgesic) and nonspecific feelings of discomfort. We will collect data on rare but serious adverse events such as seizures (reported at 1.4%).

14.3. The safety data will be reviewed on an ongoing basis during enrollment and conduct of the study.

14.4. We plan to follow the most recent safety recommendations from expert consensus panels on rTMS.

14.5. We have no planned formal analysis of the safety data.

14.6. N/A

14.7. We will follow all local and national regulations regarding the reporting of adverse events and serious adverse events.

15. Withdrawal of Subjects

15.1. The PI may remove a subject from the study at any time if he/she believes that continuing in not in his/her best medical interests, or if he/she is unable to comply with the requirements of the study.

15.2. N/A

15.3. N/A

15.4. If a subject withdraws from the study, they will be asked if they would like to allow us to keep data that has already been collected. If they do not wish for this to happen, we will get rid of any CRFs by secured document-shredding methods and remove all data on that participant from our secured database.

15.5. The participant will need to speak with either the PI or research coordinator to verify they do not want to continue participating. There will be nothing in the consent to limit a participant from voluntary withdrawal.

16. Data Management/Confidentiality

16.1. Information and clinical data collected as part of this study will be labeled with the subject's initials and study number, which will be in a locked file cabinet in the PI's office that can be locked as well.

16.2. This research does not require direct identifiers such as name or address to be used.

16.3. This research does not require the access, use, or disclosure of Protected Health Information.

16.4. This research will ask about substance abuse as it is an exclusion criterion for this project, but we will not maintain any data or information with details about potential abuse.

16.5. We will not use a Certificate of Confidentiality to protect data.

16.6. Data (without identifiers) will be entered into a computer database and/or locked file cabinet in the PI's office. All computers with data will be password protected and databases will have no linking identifiers to the participant. All study team members have completed HIPAA training.

16.7. PI will be on-site at each study visit to ensure quality control standards are being met.

16.8. N/A

16.9. N/A

16.10. N/A

16.11. N/A

17. Data and Specimen Banking

17.1. N/A

17.2. N/A

18. Risks to Subjects

18.1. ***TMS:*** *TMS is a safe procedure that has been used on many people to study the brain. Most people do not find the stimulation painful, but occasionally strong contractions of scalp muscles can cause some discomfort of headache. Headaches usually go away promptly with nonprescription medication. The noise of the TMS magnet may affect hearing, so participant will be fitted with earplugs. Magnetic stimulation will not be performed in people who have pacemakers, implanted pumps or stimulators, or who have metal objects inside the eye or skull. The risk of inducing a seizure with single, or paired-pulse, TMS is considered very low. Seizures from single/paired-pulse TMS have only been reported in subjects with medically-intractable epilepsy very rarely (0.0-3%). Safety studies using TMS in patients with neurological disorders have demonstrated no permanence.*

tDCS: *At the beginning of tDCS most people feel a tingling sensation that is present for a short period of time. Also, most people feel a warming sensation on the scalp that disappears after awhile. tDCS is known to be a safe procedure for several hundred patients at UNM, but in a few cases (1%) subjects have reported minor skin burns at the electrode spot. For example, a few subjects who had recently shaved their heads have reported transient redness and irritation at the stimulating electrode site. Prior to stimulation, your scalp will be checked for any redness or recent shaving of the head. If any of these are seen, we will pause or stop your participation in the study. You will be encouraged at the beginning of and throughout the tDCS procedure to report any pain or problems at the electrode sites that you may encounter throughout the procedure. Any problems, orevidence of redness or pain of the scalp, will result in the immediate stopping of stimulation. As with any contact between persons and electrical apparatuses, there is a slight possibility of electrical shock. To our knowledge, no studies have reported any electrical shock resulting from tDCS, and we do not expect this event to occur in our experiment. tDCS uses rubber electrode holders. If you think you may be sensitive or allergic to rubber or latex, please tell us before the start of the experiment. A few people in other studies have experienced drowsiness, excitement, or dizziness after tDCS.*

Risks of Research: *A potential loss of confidentiality, which could result in stress, emotional distress, inconvenience, and possibly loss of privacy.*

18.2. N/A

18.3. As risk to fetus by TMS is not known, we will not include pregnant women in this study. We will administer a pregnancy test to any women of childbearing potential at each visit and with confirmation that the test is negative before study procedures ensue.

18.4. N/A

18.5. As noted, women of childbearing potential will be tested for pregnancy prior to treatment. Participants with a pre-existing seizure disorder, or who meet criteria that may increase likelihood of seizure will be excluded from the study. Our study team will take all necessary measures to minimize the risk of loss of confidentiality by following all procedures noted in this protocol.

19. Potential Benefits to Subjects

19.1. There is potential societal benefit in understanding the brain mechanisms underlying metaplasticity and has implications in both health and disease.

19.2. There is no direct benefit to subjects for participating in this study.

20. Recruitment Methods

20.1. Participants will be recruited beginning upon IRB approval for this project. We will utilize both fliers posted around the North and Main campus of UNM as well as the healthy participant registry at the CTSC.

20.2. We will not reviewing any participant medical charts.

20.3. We will utilize a flier that describes the purpose and scope of this study, it will list an email and phone contact for interested subjects to get in touch with us.

21. Provisions to Protect the Privacy Interests of Subjects

21.1. Subjects will be completing the study visit, including consent and giving any necessary information in our secured noninvasive neurostimulation lab. The nature of the information they may need to provide includes basic demographics and health history. We will inform the subject that only members of the study team may access any of their information and data.

21.2. Any recruitment phone calls will be taken on a landline in the research coordinator's lab space. The consent and data collection process will be done in a lab that has a closed door and will not be access by anyone outside of the study team. Once data is collected we will follow all procedures described in the protocol, which will be explained to the participant as well, and will include password-protected databases and locked file cabinets in private offices.

22. Economic Burden to Subjects

22.1. N/A

Research Procedures	Number of Samples/Procedures	Responsible Party	
		Study	3rd Party Payer or Participant
rTMS	3	☒	☐
tDCS	3	☒	☐
Pregnancy test	1	☒	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
Standard of Care Procedures	**Number of**	**Responsible Party**	

	Samples/Procedures	Study	3rd Party Payer or Participant
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐

22.2. N/A

22.3. N/A

22.4. We will explain to the participant, and also note in the consent form, that if an adverse event occurs the participant will be able to receive treatment here at UNMH but that it will be at the expense of the participant and that we are not liable for any costs incurred.

22.5. N/A

23. Compensation

23.1. In return for a subject's time and inconvenience due to participating in clinical research, he/she will be compensated a total of $70 for the whole study in the form of a merchandise cards.

They will receive $20 for each of the first 2 study visits (subtotal $40). They will receive $30 for the last study visit (subtotal $30 plus first 2 visit subtotal = $70).

This amount is appropriate for the time and inconvenience of the proposed research and would not be construed as coercive nor would the small increase for the last visit unduly induce subjects to remain in the study when they otherwise would have withdrawn.

24. Compensation for Research-Related Injury

24.1. N/A

24.2. We will explain to the participant, and also note in the consent form, that if an adverse event occurs the participant will be able to receive treatment here at UNMH but that it will be at the expense of the participant and that we are not liable for any costs incurred.

25. Consent Process

25.1. We will be obtaining informed consent from each subject prior to study participation. The consent form will discuss the purpose and scope of the study, the procedures that will be performed, and the risks/benefits associated with the study. We will give the subject a copy of the signed consent form. We will allow

plenty of time for the subject to make a decision and ask any questions they may have before consent, as well as throughout the study.

25.1.1. The PIs, Co-I and research coordinator will be responsible for obtaining consent and they have completed the requisite training.

25.1.2. The consent process will take place in our noninvasive neurostimulation lab in the CTSC, which is a private and secure location.

25.1.3. This study does not offer any significant benefit to the subject, and they will not be compensated at an amount that may be perceived as coercive. We will be sure to inform the subject that the study is entirely voluntary, and will not way inhibit any current or future care they receive from us here at UNM.

25.1.4. If the subject is interested, we will e-mail them a copy of the consent prior to their participation so that they have time to fully review. Regardless, we will take our time walking them through the consent and allow as much time as is needed for questions. We will also let them know that they are welcome to take the consent home to discuss with friends or family.

25.1.5. We will encourage the subject to ask questions throughout the study, and will check in to ensure they are comfortable and feel safe. If subject seems uncertain or hesitant, we will remind them that they are welcome to stop participation at any time with no consequences.

25.1.6. We will allow for a question and answer period to enhance understanding.

25.1.7. We will not ask the participant to teach back specifically, unless they have questions that lead us to believe they do not fully understand, or seem hesitant or uncertain.

Subjects not fluent in English

25.1.8. N/A

25.1.9. N/A

25.1.10. N/A

Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally Authorized Representative

25.1.11. N/A

25.1.12. N/A

25.1.13. N/A

25.1.14. N/A

25.1.15. N/A

25.1.16. N/A

25.1.17. N/A

25.1.18. N/A

25.1.19. N/A

25.1.20. N/A

Subjects who are not yet adults (infants, children, teenagers)

25.1.21. N/A

25.1.22. N/A

25.1.23. N/A

25.1.24. N/A

25.1.25. N/A

25.1.26. N/A

25.1.27. N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required element of consent will not be included, or one or more required elements of consent will be altered)

- *N/A*

26. Documentation of Consent

26.1. We do plan to use a consent form to document informed consent. It is attached to the new study application.

26.2. N/A

26.3. N/A

27. Study Test Results/Incidental Findings

27.1. ***Individual Results:*** *We do not intend to share study test or procedure results with study participants with the exception of the results of the pregnancy test. This result will be communicated in person as well as through mail notification.*

27.2. ***Incidental Findings:*** *We do not anticipate that the research may result in incidental findings.*

28. Sharing Study Progress or Results with Subjects

28.1. We do not intend to provide subjects with a summary of the trial progress while the study remains underway.

28.2. We do not intend to provide subjects with a summary of the study results after the study is complete. We do intend to disseminate the results through peer-reviewed publication and presentation at national meetings.

29. Inclusion of Vulnerable Populations

29.1. N/A

30. Community-Based Participatory Research

30.1 N/A

31. Research Involving American Indian/Native Populations

31.1 N/A

32. Transnational Research

32.1. N/A

32.2. N/A

32.3. N/A

32.4. N/A

32.5. N/A

32.6. N/A

33. Drugs or Devices

33.1. This study utilizes a Magstim Rapid2 rTMS device (The Magstim Company Limited, Spring Gardens, Whitland, Carmarthenshire, SA34 0HR, UK). This device is FDA approved for the treatment of treatment-resistant depression and has been approved for treatment of Migraine. The UNM HRRC has previously determined that TMS devices are not significant risk and has also been determined by the sponsor-investigator (Sarah Pirio Richardson, MD) to be a Non-Significant Risk device. The device is already housed at UNM in the Noninvasive Neurostimulation Lab, and access will be limited to the PI who is fellowship trained in operating these devices and to study personnel who she trains to use these devices safely.

The TDCS device utilized in this study is determined to be a Non-Significant Risk device by the sponsor-investigator (Davin Quinn, MD) for the following reasons:

1) It is not intended as an implant

2) It does not present a potential for serious risk to the health, safety, or welfare of the subjects

3) It is not proposed to be for a use in supporting or sustaining human life

4) It is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or preventing impairment of human health

According to the FDA, serious adverse events are those in which the outcome is death, life-threatening, hospitalization, disability/permanent damage, congenital anomaly, requiring intervention to prevent permanent impairment, or other serious events such as refractory seizures, cardiorespiratory arrest, or anaphylactic reaction. No serious adverse events attributable to TDCS have been reported in the more than 10,000 subjects investigated in the contemporary TDCS literature since 1998. This literature includes studies in patients with severe brain injury, stroke, epilepsy, and neurodegenerative

disorders, none of whom have been reported to experience serious adverse events. Specifically, there have been no reports or evidence presented of damage to the brain, seizures, or cardiorespiratory arrest. Animal studies of charge densities necessary to induce brain damage in rats were found to be 100 times higher than the charge density used in TDCS trials with standard parameters (< 2.5 mA, no more than 2 sessions daily, < 60 min per session, use of electrodes that minimize skin burns) as determined by world-wide expert consensus. The commonly reported side effects of TDCS are itching, burning, tingling, headache, and discomfort (10-40%), all of which are mild and transient. As this trial will be operating within standard parameters as defined above, we believe our use of TDCS in subjects represent a Non-Significant Risk.

33.2. N/A

33.3. N/A

33.4. The "Device Checklist" in the Checklist Section of this template has been completed.

Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

A. Partial Waiver of Consent for Screening/Recruitment

Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.

1. Describe the data source that you need to review (e.g., medical records):

2. Describe the purpose for the review (e.g., screening):

3. Describe who will conducting the reviews (e.g., investigators, research staff):

4. Do all persons who will be conducting the reviews already have permitted access to the data source?

   ☐ Yes

   ☐ No. Explain:

5. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:

   a) <u>The activity involves no more than minimal risk to the subjects</u> because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.

      ☐ True

      ☐ Other justification:

   b) <u>The waiver or alteration will not adversely affect the rights and welfare of the subjects</u> because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).

      ☐ True

☐ Other justification:

c) The research could not practicably be carried out without the waiver or alteration because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.

☐ True

☐ Other justification:

d) Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)*

☐ True

☐ Other justification:

Partial Waiver of HIPAA Authorization for Screening/Recruitment
Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

6. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   ☐ Yes. Describe:

   ☐ No

7. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

8. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☐ True

   ☐ False

B. Waiver of Documentation of Consent

Complete this checklist if you intend to obtain consent verbally but will not be obtaining signatures from subjects on a consent form to document consent. Waivers of documentation of consent are commonly requested when using scripts, information sheets, or email or survey introductions to present the elements of consent instead of using a traditional consent form.

1. Are you requesting a waiver of documentation of consent for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Provide justification for one of the following:

   a) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

   b) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

3. Do you intend to provide subjects with a written statement regarding the research in lieu of a traditional consent form?

   ☐ Yes. Please attach a copy to your submission in Click.

   ☐ No

C. Alteration of Consent

Complete this checklist if you intend to obtain consent but will be eliminating or altering one or more of the required elements of consent. Alterations of consent are commonly requested for research involving deception or for minimal risk research when an abbreviated consent is desired and one or more of the required element are not relevant to the research.

Note: FDA-regulated research is not eligible for an alteration of consent.

1. Which element(s) of consent do you wish to eliminate and why?

2. Which element(s) of consent do you wish to alter and why?

3. Provide justification for each of the following regulatory criteria:
   a) The research involves no more than minimal risk to the subjects:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

   c) The research could not practicably be carried out without the waiver or alteration:

   d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

D. Full Waiver of Consent/Parental Permission

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of consent are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

Note: FDA-regulated research is not eligible for a full waiver of consent using these criteria. If you believe that your FDA-regulated research may be eligible for a waiver under another mechanism, such as planned emergency research, contact the HRPO for assistance in determining what information to provide to the HRRC.

1. Are you requesting a waiver for some or all subjects?
   ☐ All
   ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:
   a) The research involves no more than minimal risk to the subjects:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

c) The research could not practicably be carried out without the waiver or alteration:

d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

E. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs)

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort) and the research involves the evaluation of a public benefit or service program.

1. Are you requesting a waiver for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:

   a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs:

   b) The research could not practicably be carried out without the waiver or alteration.

F. Full Waiver of HIPAA Authorization

Complete this checklist if you are requesting a full waiver of the requirement to obtain HIPAA authorization for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of HIPAA authorization are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

1. Are you requesting a waiver of authorization for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Describe your plan to protect health information identifiers from improper use and disclosure:

3. Describe your plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so):

4. Describe why the research could not practicably be conducted without the waiver or alteration:

5. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☐ True

   ☐ False

G. Other Waiver Types

If you are seeking another waiver type (e.g., Planned Emergency Research, Waiver of Parental Permission to Protect Child Participants, Enforcement Discretion for In Vitro Diagnostics, etc. contact the HRPO office for assistance in determining what information to submit for the HRRC's consideration.

II. Vulnerable Populations

A. Adults with Cognitive Impairments

Complete this checklist if the subject population will include adults with cognitive impairments.

This checklist does not need to be completed if the research doesn't involve interactions or interventions with subjects and will be conducted under a waiver of consent.

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.

2. Describe how capacity to consent will be evaluated.

3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.

4. Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.

5. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.

6. Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.

7. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.

8. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

B. Children

Complete this checklist if the subject population will include children.

1. Select the category of research that you believe this research falls within and provide justification for any associated criteria. If there are different assessments for different groups of children or arms (e.g., placebo vs. drug), include a memo to provide an assessment for each group.

   ☐ Research not involving greater than minimal risk. *(Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.)*

☐ Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Provide justification for each of the following criteria:

(1) The risk is justified by the anticipated benefit to the subjects:

(2) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches:

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

Provide justification for each of the following criteria:

(1) The risk represents a minor increase over minimal risk:

(2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations:

(3) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition

C. Pregnant Women and Fetuses

Complete this checklist if the subject population will include pregnant women and fetuses.

This checklist does not need to be completed if the research is both minimal risk and is not conducted, funded, or otherwise subject to regulation by DHHS, DOD, EPA, or VA.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; ***or***, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

3. Any risk is the least possible for achieving the objectives of the research.

D. Neonates of Uncertain Viability or Nonviable Neonates
Complete this checklist if the subject population will include neonates of uncertain viability.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, ***or***, the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research

E. Nonviable Neonates
Complete this checklist if the subject population will include nonviable neonates.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

Verify each of the following:

5. Vital functions of the neonate will not be artificially maintained

☐ True

☐ False

6. The research will not terminate the heartbeat or respiration of the neonate

☐ True

☐ False

7. There will be no added risk to the neonate resulting from the research

☐ True

☐ False

F. Biomedical and Behavioral Research Involving Prisoners

Complete this checklist if the subject population will include prisoners.

Note: Minimal risk for research involving prisoners is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

1. Select and justify which allowable category of research involving prisoners this research falls within:

☐ Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

☐ Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

☐ Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults)

☐ Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject

☐ Epidemiologic studies in which the sole purpose is to describe the prevalence or incidence of a disease by identifying all cases or to study potential risk factor associations for a disease, the research presents no more than Minimal Risk and no more than inconvenience to the subjects, and Prisoners are not a particular focus of the research.

2. Provide justification for each of the following regulatory criteria:

    a) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired

    b) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers

    c) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless justification is provided, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project

d) The information is presented in language which is understandable to the subject population

e) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole

f) When appropriate, adequate provision has been made for follow up examination or care after research participation, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact

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III. Medical Devices

Complete this checklist if the research evaluates the safety or effectiveness of a medical device. If more than one medical device is being evaluated, provide the requested information for each.

A. Device Name: *Magstim Rapid2 rTMS device*

B. Manufacturer: *The Magstim Company Limited, Spring Gardens, Whitland, Carmarthenshire, SA34 0HR, UK*

C. Does the research involve a Significant Risk Device under an IDE?

☐ Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number and approval status; (2) Industry sponsor letter noting IDE number and FDA approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted*

☒ No

D. Is the research IDE-exempt?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*.

☒ No

E. Does the research involve a Non-Significant Risk (NSR) Device?

☒ Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.

☐ No

F. Device Name: *MR transcranial electrical stimulator*

G. Manufacturer: *NeuroConn*

H. Does the research involve a Significant Risk Device under an IDE?

☐ Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number and approval status; (2) Industry sponsor letter noting IDE number and FDA approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted*

☒ No

I. Is the research IDE-exempt?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*.

☒ No

J. Does the research involve a Non-Significant Risk (NSR) Device?

☒ Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.

☐ No

* This FDA guidance includes a description for when a device study is exempt from the IDE requirements:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

**This FDA guidance includes information on how to differentiate between Significant Risk and Non-Significant Risk device studies:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf