Study Protocol

Repeated Transcranial Magnetic Stimulation and Rehabilitation for Individuals with Complex Regional Pain Syndrome Type 1

PROTOCOL TITLE:

Repeated Transcranial Magnetic Stimulation and Rehabilitation for Individuals with Complex Regional Pain Syndrome Type 1.

PROTOCOL VERSION/AMENDMENT # AND DATE

Version 2, 11/08/22

PRINCIPAL INVESTIGATOR:

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives of this research. Specifically, explain why it is important to do the study.

The purpose of this study is to investigate the effectiveness of rTMS combined with rehabilitation in patients with complex regional pain syndrome type 1 (CRPS). CRPS is associated with pain, disability, psychological distress, and social interference.[1,2] The disorder is difficult to treat and often leads to long-term problems. Several interventions are recommended including medication, rehabilitation, cognitive/psychological interventions, and invasive pain management devices such as dorsal column root stimulators.[3] Despite these interventions, many individuals have persistent pain and disability. Recent studies have investigated rTMS as an intervention for painful conditions that have a poor response to other treatments.[4,5] These studies suggest that rTMS leads to reduced pain in the short-term. Three studies have used rTMS to treat patients with CRPS with promising short-term results.[5–7] There have been no studies looking at the impact of combining rTMS with high-quality rehabilitation. Combining rTMS and high-quality rehabilitation may lead to better short-term and long-term outcomes. The aims of this study are:

1: Determine the short-term effects of rTMS and rehabilitation on pain intensity, pain interference, physical function, fatigue, depression, anxiety, and satisfaction with participation in social roles.

2: Determine the long-term effects of rTMS and rehabilitation on pain intensity, pain interference, physical function, fatigue, depression, anxiety, and satisfaction with participation in social roles.

1. Cossins L, Okell RW, Cameron H, Simpson B, Poole HM, Goebel A. Treatment of complex regional pain syndrome in adults: a systematic review of randomized controlled trials published from June 2000 to February 2012. *Eur J Pain*. 2013;17(2):158-173. doi:10.1002/J.1532-2149.2012.00217.X

2. Prasad, MD A, Chakravarthy, MD K. Review of complex regional pain syndrome and the role of

the neuroimmune axis. *Mol Pain*. 2021;17. doi:10.1177/17448069211006617

3. O'Connell NE, Wand BM, Mcauley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews. *Cochrane Database Syst Rev*. 2013;2013(4). doi:10.1002/14651858.CD009416.pub2

4. Sun P, Fang L, Zhang J, Liu Y, Wang G, Qi R. Repetitive transcranial magnetic stimulation for fibromyalgia patients: A Systematic Review with Meta-Analysis. *Pain Med*. Published online September 20, 2021. doi:10.1093/PM/PNAB276

5. Picarelli H, Teixeira MJ, De Andrade DC, et al. Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. *J pain*. 2010;11(11):1203-1210. doi:10.1016/J.JPAIN.2010.02.006

6. Gaertner M, Kong JT, Scherrer KH, Foote A, Mackey S, Johnson KA. Advancing Transcranial Magnetic Stimulation Methods for Complex Regional Pain Syndrome: An Open-Label Study of Paired Theta Burst and High-Frequency Stimulation. *Neuromodulation*. 2018;21(4):409-416. doi:10.1111/NER.12760

7. Pleger B, Janssen F, Schwenkreis P, Völker B, Maier C, Tegenthoff M. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. *Neurosci Lett*. 2004;356(2):87-90. doi:10.1016/J.NEULET.2003.11.037

1.2 State the hypothesis to be tested, if applicable.
NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.

H: Subjects with CRPS treated with rTMS and rehabilitation will have better outcomes than subjects treated with sham rTMS and rehabilitation.

2.0 Scientific/Safety Endpoints

2.1 Describe the scientific endpoint(s), the main result or occurrence under study.
NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should not be a date.

Endpoints:

1- The pilot stage of the project will be complete after 12 subjects or 4 months, whichever comes first. At this point, adjustments will be made to the protocol and recruitment strategies as needed. Any changes will be submitted to the IRB for approval.
2- Stage two of the study will continue until a total of 20 subjects have completed the testing, or 30 total subjects have been enrolled. If 30 subjects have been enrolled, but less

than 20 subjects have completed the protocol the authors will re-assess the study methods and consider amending the IRB protocol to include more than 30 subjects.

3- The study may be stopped if there is no new enrollment in the study for up to 6-months.
4- The study will be stopped after the pilot stage if more than 30% of subjects withdraw from the study due to side effects or excessive burden from the treatment protocol.

3.0 Background

3.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute/fill in gaps to existing knowledge.

Complex regional pain syndrome type 1 is a chronic condition that includes sensory, motor, vasomotor, autonomic, and tissue dysfunction.[1,2] Symptoms include pain, swelling, stiffness, weakness, and skin changes.[3] The disorder primarily impacts the extremities with 59% of the cases involving the upper extremity.[2] The precise incidence rate is unclear and has been reported to be between 2.16-40.4 per 100,000 person years.[24] CRPS impacts women 4 times more than men and the most common precipitating event is a fracture.[4,5] The long-term impact of CRPS is uncertain and it is common for individuals to have long-lasting symptoms. Sandroni et al identified 74 cases of CRPS in Olmsted County (Minnesota, population of 106,470) and found a resolution rate of 74% with a range of 1-60 months.[4] In, contrast, Schwartzman et al looked at 656 patients with CRPS of at least 1-year and found a 0% resolutions rate.[3] This suggests that CRPS symptoms lasting more than a year are unlikely to resolve.

Literature on the effectiveness of treatments for patients with CRPS is limited and often of low quality. Systematic reviews and guidelines support the use of education, medication, and rehabilitation involving graded motor imagery as first-line interventions.[1,6,7] These interventions appear to be effective for some individuals, but effect sizes are small and they do not provide a meaningful reduction in symptoms for a significant number of patients.[1,8] Second-line treatments include injections and implantable neuromodulation devices.[1,6,9] There is limited evidence for the effectiveness of these interventions and they can be associated with adverse events such as infection, lead migration, and device failure. [1,9]

Given the lack of highly effective interventions for CRPS there is a need for better treatment approaches. rTMS is a treatment of interest for several chronic pain conditions that are resistant to other treatment modalities. The mechanism(s) behind the analgesic effects of rTMS are not completely understood but it is thought to include changes in neuronal excitation and increased plasticity.[10,11] Studies have found rTMS to be an effective intervention for peripheral neuropathy and fibromyalgia.[11–16] Most of these studies have only looked at short-term effects but reduced pain up to 4 weeks has been seen.[11,17] Three studies have investigated the use of rTMS in patients with persistent CRPS symptoms. All three studies found positive short-term

effects with 51-70% of subjects reporting pain relief.[18–20] These studies suggest that rTMS may improve the outcomes of patients with CRPS, but the long-term effects are unknown.

In our study, we will look at the combined impact of rTMS and rehabilitation on the outcomes of patients with CRPS. It is hypothesized that rTMS may create a window of reduced pain and increased neural plasticity that magnifies the long-term effects of rehabilitation aimed at cortical reorganization and behavior modification. Graded Motor Imagery (GMI) is a three-part treatment that targets the cortical reorganization that may perpetuate symptoms associated with CRPS.[21–23] Combining GMI with rTMS may lead to greater changes in cortical reorganization and result in longer-lasting symptoms reduction. Graded exercise and graded activity are common rehabilitation strategies aimed at behavioral changes. By slowly progressing physical activity patients build a "tolerance" that allows them to function at a higher level.[24] The pain relief caused by rTMS may help patients better tolerate these graded approaches leading to long-term functional improvement.

3.2 Include complete citations or references:

1. O'Connell NE, Wand BM, Mcauley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews. *Cochrane Database Syst Rev*. 2013;2013(4). doi:10.1002/14651858.CD009416.pub2
2. de Mos M, de Bruijn A, Huygen F, Dieleman J, Stricker Bhc, Sturkenboom M. The incidence of complex regional pain syndrome: A population-based study. doi:10.1016/j.pain.2006.09.008
3. Schwartzman RJ, Erwin KL, Alexander GM. The natural history of complex regional pain syndrome. *Clin J Pain*. 2009;25(4):273-280. doi:10.1097/AJP.0B013E31818ECEA5
4. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain*. 2003;103(1-2):199-207. doi:10.1016/S0304-3959(03)00065-4
5. Harden RN, Oaklander AL, Burton AW, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. *Pain Med*. 2013;14(2):180-229. doi:10.1111/PME.12033
6. Goebel A, Barker C, Turner-Stokes L, Cameron H, Cohen H. Complex regional pain syndrome in adults (2nd edition) | RCP London. *London RCP*. Published online 2018. Accessed December 10, 2021. https://www.rcplondon.ac.uk/guidelines-policy/complex-regional-pain-syndrome-adults
7. Cossins L, Okell RW, Cameron H, Simpson B, Poole HM, Goebel A. Treatment of complex regional pain syndrome in adults: a systematic review of randomized controlled trials published from June 2000 to February 2012. *Eur J Pain*. 2013;17(2):158-173. doi:10.1002/J.1532-2149.2012.00217.X
8. Prasad, MD A, Chakravarthy, MD K. Review of complex regional pain syndrome and the role of the neuroimmune axis. *Mol Pain*. 2021;17. doi:10.1177/17448069211006617
9. Deer TR, Grider JS, Lamer TJ, et al. A Systematic Literature Review of Spine Neurostimulation Therapies for the Treatment of Pain. *Pain Med*. 2020;21(7):1421-1432. doi:10.1093/PM/PNZ353

10. Lefaucheur JP, André-Obadia N, Antal A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol*. 2014;125(11):2150-2206. doi:10.1016/J.CLINPH.2014.05.021
11. Hamid P, Malik BH, Hussain ML. Noninvasive Transcranial Magnetic Stimulation (TMS) in Chronic Refractory Pain: A Systematic Review. *Cureus*. 2019;11(10):e6019. doi:10.7759/cureus.6019
12. Sun P, Fang L, Zhang J, Liu Y, Wang G, Qi R. Repetitive transcranial magnetic stimulation for fibromyalgia patients: A Systematic Review with Meta-Analysis. *Pain Med*. Published online September 20, 2021. doi:10.1093/PM/PNAB276
13. Su Y-C, Guo Y-H, Hsieh P-C, Lin Y-C. Efficacy of Repetitive Transcranial Magnetic Stimulation in Fibromyalgia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Clin Med*. 2021;10(20). doi:10.3390/jcm10204669
14. Passard A, Attal N, Benadhira R, et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. *Brain*. 2007;130(10):2661-2670. doi:10.1093/brain/awm189
15. Lefaucheur JP, Drouot X, Ménard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. *Neurology*. 2006;67(9):1568-1574. doi:10.1212/01.wnl.0000242731.10074.3c
16. Lefaucheur JP. The use of repetitive transcranial magnetic stimulation (rTMS) in chronic neuropathic pain. *Neurophysiol Clin*. 2006;36(3):117-124. doi:10.1016/J.NEUCLI.2006.08.002
17. Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. *J Neurol Neurosurg Psychiatry*. 2005;76(6):833-838. doi:10.1136/JNNP.2004.055806
18. Pleger B, Janssen F, Schwenkreis P, Völker B, Maier C, Tegenthoff M. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. *Neurosci Lett*. 2004;356(2):87-90. doi:10.1016/J.NEULET.2003.11.037
19. Picarelli H, Teixeira MJ, De Andrade DC, et al. Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. *J pain*. 2010;11(11):1203-1210. doi:10.1016/J.JPAIN.2010.02.006
20. Gaertner M, Kong JT, Scherrer KH, Foote A, Mackey S, Johnson KA. Advancing Transcranial Magnetic Stimulation Methods for Complex Regional Pain Syndrome: An Open-Label Study of Paired Theta Burst and High-Frequency Stimulation. *Neuromodulation*. 2018;21(4):409-416. doi:10.1111/NER.12760
21. Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. *Pain*. 2004;108(1-2):192-198. doi:10.1016/J.PAIN.2004.01.006
22. Moseley GL. Is successful rehabilitation of complex regional pain syndrome due to sustained attention to the affected limb? A randomised clinical trial. *Pain*. 2005;114(1-2):54-61. doi:10.1016/J.PAIN.2004.11.024
23. Moseley GL. Graded motor imagery for pathologic pain: A randomized controlled trial. *Neurology*. 2006;67(12):2129-2134. doi:10.1212/01.wnl.0000249112.56935.32
24. Shepherd M, Louw A, Podolak J. The clinical application of pain neuroscience, graded

motor imagery, and graded activity with complex regional pain syndrome-A case report. *Physiother Theory Pract*. 2020;36(9):1043-1055. doi:10.1080/09593985.2018.1548047

4.0 Study Design

4.1 Describe and explain the study design (e.g. case-control, cross-sectional, experimental, interventional, longitudinal, and observational). Indicate if there is randomization, blinding, control group, etc. If randomizing, explain how this will be achieved. For studies that have a complex study design (i.e., multiple arms and treatments), include a schematic diagram.

This study will have a pilot phase and a randomized phase. The pilot phase will include 1-3 subjects who will receive real rTMS and rehabilitation. Subjects in the placebo controlled randomize phase will receive rehabilitation combined with either real or sham rTMS. Randomization will be performed in REDCap and be stratified by upper or lower extremity. Randomization will occur in blocks of 4 to ensure equal distribution. Patients and the physical therapists delivering rehabilitation will be blinded to group allocation (real/sham rTMS). The researcher administering the rTMS will not be blinded.

Changes included in protocol version 2:

- Addition of new advertisement document that will be handed out by clinicians to potential subjects.
- Addition of a pilot phase that will include 1-3 unrandomized subjects.
- Adjusted the subject numbers to reflect the pilot phase subjects.
- Added Joseph Defelice to the study team.
- Created new informed consent document for the pilot phase.

5.0 Data Management and Analysis

5.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis

1) Primary: NPRS weekly average: 2-way ANOVA for within and between effects.

Secondary:

2) NPRS worse/least 24 hours: 2-way ANOVA for within and between effects.
3) NPRS number reaching 30% improvement: Descriptive (%), Logistic Regression
4) PROMIS: 2-way ANOVA for within and between effects.
    a. Pain interference
    b. Pain behavior
    c. Physical functioning

d. Satisfaction with discretionary social activity
e. Satisfaction with social roles
f. Fatigue
g. Depression
h. Anxiety
i. Anger

5) GROC: 2-way ANOVA for within and between effects.
6) GROCi: 2-way ANOVA for within and between effects.
7) PASS: Logistic Regression
8) Grip Strength: 2-way ANOVA for within and between effects.
9) 1 Repetition Max Leg Press: 2-way ANOVA for within and between effects.

5.2 If applicable, provide a power analysis for the number of subjects to be included. If qualitative research, so state, and provide general justification for the total number of subjects proposed.

NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.

The pain numeric rating scale (NPRS) MCID ranges from 1 to 2.5 in the literature. Salaffi et al (2003) found that a reduction of 2.0 points was associated with a rating of "much better" for patients with chronic pain. A review of the literature looking at pain ratings for patients with CRPS showed standard deviations approximately 1.0 to 2.0. Effect size was calculated using a 2-point NPRS change and a standard deviation of 1.7. G*Power 3.1.9.7 was used to calculate the sample size based on a repeated measures ANOVA with between and within measures comparisons . A partial n^2 of .07 (moderate effect size) gave an effect size of .274, a=0.05, and power was set at 80%. Sample size was calculated for 2 groups, 4 measurements, with a correlation of .5, and nonsphericity of 1. This resulted in a group size of 10 participants for a total of 20 subjects. To account for dropouts up to 36 subjects will be enrolled in this study.

6.0 Local Number of Subjects

6.1 Indicate the total number of subjects who will be enrolled or records that will be reviewed through Upstate.

Based on the power analysis and overage for dropouts a maximum of 33 subjects will be enrolled in the study. The goal is to have at least 20 subjects complete all testing.

6.2 If applicable, indicate your screen failure rate, i.e., how many subjects you expect to screen to reach your target sample.

We are attempting to keep the inclusion/exclusion criterion broad and we are including patients with upper and lower extremity symptoms. After phase one of this project, we will have a better idea of the screening failure rate. Given the lack of alternative treatments for this condition and the impact symptoms can have on quality of life, we feel that potential subjects will be highly motivated to be involved in the study.

6.3 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Recruitment for this study may be challenging due to the rarity of the condition. We are partnered with the Upstate PM&R department who routinely see patients with this condition. We will also send recruitment materials to pain management specialists and surgeons inside and outside the Upstate system.

7.0 Inclusion and Exclusion Criteria

7.1 Describe, in bullet points, the criteria that define who will be included in this study:

Eligible subjects will meet all of the following criteria:

1) 18 years or older
2) Upper or lower extremity CRPS Type 1 (also called RSD-Reflex Sympathetic Dystrophy) of at least 6 months. It is anticipated that most potential subjects will have an established diagnosis of CRPS by a healthcare provider. Study members will confirm the diagnosis by using the Budapest Criteria, which is the most current diagnostic criterion for CRPS.
    a. Budapest Criteria- To be diagnosed with CRPS individuals must have continued pain, which is disproportionate to inciting event, no other diagnosis that better explains the symptoms and 1 symptom in 3 of the 4 categories and 1 sign in 2 of the 4 categories below.
        i. Sensor-hyperalgesia and/or allodynia
        ii. Vasomotor-temperature asymmetry, skin color changes or asymmetry
        iii. Sudomotor/Edema-Edema and/or sweating changes and/or sweating asymmetry
        iv. Motor/trophic-reduced ROM, weakness, tremor, dystonia, or changes in hair, nail, or skin.
3) Pain rating on NPRS of at least 4/10
4) No initiation of a new intervention (i.e., medication, rehab, injections) in the previous 2 months.

5) No plan to initiate a new intervention during the study treatment timeframe (4 weeks).

7.2 Describe, in bullet points, the criteria that define who will be excluded from this study:

Potential subjects with any of the following will be excluded.
1) A history of seizures or epilepsy
2) Intracranial metallic devices
3) Pacemaker
4) Intrathecal infusion pumps
5) Brain or spinal cord stimulators with epidural electrodes
6) Other ferromagnetic metallic intracranial implants
7) Apparent mental or psychiatric disorder that prevents adequate informed consent
8) Current pregnancy
9) Non-English speaking

7.3 Indicate whether you are specifically recruiting or targeting any of the following special populations in your study using the checkboxes below.

N/A

☐ Adults unable to consent (*complete and upload Supplemental Form A)*
☐ Minors (under 18 years old)
☐ Pregnant women
☐ Prisoners

6.4 Indicate if you will include minorities (American Indians, Alaskan Native, Asian, Native Hawaiian, Pacific Islander, Black [not of Hispanic origin] and Hispanic) as Federal mandates require that you include minorities unless you can justify their exclusion

☒ Yes
☐ No, Justify:

8.0 Vulnerable Populations

8.1 For research that involves pregnant women, review, complete and upload Supplemental Form B: Research Involving Pregnant Women, Fetuses, or Neonates.

☐ Confirmed
☒ N/A: This research does not involve pregnant women.

8.2 For research that involves neonates of uncertain viability or non-viable neonates, review, complete and upload Supplemental Form B: Research involving Pregnant Women, Fetuses, or Neonates.

☐ Confirmed

☒ N/A: This research does not involve non-viable neonates or neonates of uncertain viability.

8.3 *For research that involves prisoners, review, complete and upload Supplemental Form C: Research involving Prisoners*

☐ Confirmed

☒ N/A: This research does not involve prisoners.

8.4 For research that involves minors (under 18 years), review, complete and upload Supplemental Form D: Research involving Minors

☐ Confirmed

☒ N/A: This research does not involve minors (under 18 years),

8.5 Consider if other specifically targeted populations such as students, employees of or educationally or economically disadvantaged persons are vulnerable. Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.

☒ N/A

9.0 Eligibility Screening

9.1 *Describe screening procedures for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria. Include (upload) all relevant screening documents with your submission (e.g. screening protocol, script, questionnaires).*

Potential subjects will be screened via phone using a standardized screening document and a TMS screening questionnaire. If they meet the eligibility criterion they will be invited to participate in the study. Additional screening to confirm the diagnosis of CRPS using the Budapest criterion will be performed at the first session. On their arrival, participants will complete the same TMS questionnaire again (about 10 minute) to ensure their medical status has not changed.

☐ N/A: There is no screening as part of this protocol.

10.0 Recruitment Methods

☐ N/A: Subjects will not be recruited.

10.1 Describe source of subjects: When, where, and how potential subjects will be recruited.

NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study; for example, physician referral, database search, reviewing medical records, research participant groups/help/advocacy groups, advertising companies, call centers, in person announcements / presentations, etc.

The primary recruitment method will be through physician or other healthcare provider referral. Recruitment materials will be left with medical offices and placed in waiting rooms, when approved. Flyers, media advertisement, social media, and word of mouth will also be utilized.

10.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.

NOTE: Privacy refers to an individual's right to control access to him or herself. This is NOT asking about confidentiality of data.

The recruitment screening process will occur via phone. If the potential subject is not comfortable with a phone screening, they will be offered a private meeting. Subjects will be allowed to ask questions about the study protocol during the screening or at another time. Screening will be performed by IRB-approved study personnel, who are aware of privacy standards.

10.3 Identify all materials that will be used to recruit subjects and upload copies of these documents (such as telephone scripts, flyers, questionnaires, posters, letters, e-mails, pamphlets, advertisements).

A flyer, telephone script, tear-off pad flyer, and language to be used in a social media post were uploaded.

11.0 Research Methods & Procedures

Provide a detailed description of the methods and procedures that will be used to carry out the study. Include a summary of study visits and procedures (i.e., schedule of events table) in the space below or as an attachment.

Please make sure to include:

- Dosing of drugs and other details of study drug administration and study treatments
- A list and description of any experimental procedures
- A list and description all tests & procedures that would not be done if the subjects were not in the study
- An explanation how study participation differs from the standard of care
- Procedures being performed to monitor subjects for safety or to minimize risks

Interventions: 4 weeks

- Treatment will start (week 1) with 4 consecutive rTMS and 2 PT sessions (skipping weekends)
- Sessions will continue at 2 times a week for a total of 10 sessions
- Measurements will occur at:
  - The first visit (except GROC)
  - The last visit of each week
  - At 4 time points after the termination of the interventions-via e-mail survey
    - 4 weeks
    - 3 months
    - 6 months
    - 1 year

First Session:

- Screening (Budapest Criterion, and TMS screening)
- Informed consent- during the phone screening subjects will be given the opportunity to have informed consent documents sent to them via email. Subjects will be given time to read the documents and ask questions about the study before agreeing to participate.
- Randomization
- Baseline measurements
- rTMS/sham rTMS session
- PT session

Subsequent Sessions (9):

- TMS screening
- rTMS/sham rTMS (the first week 2/4 sessions will not include a PT session)
- PT session
- Repeat measurements will be taken at the end of each week (4 in total)

Test and measures: All outcome measures are self-reported and collected using REDCap.

- Primary
  - Numeric Pain Rating Scale (NPRS) (0-10): Average score for the week

- Secondary Measures
    - Numeric Pain Rating Scare (0-10): Worse and least pain intensity over past 24 hours
    - NIH Patient-Reported Outcomes Measurement Information System (PROMIS): Pain interference, pain behavior, physical functioning, satisfaction with discretionary social activity, satisfaction with social roles, fatigue, depression, anxiety, and anger.
    - Patient Global Impression of Change (GROC) (only measured at follow-up)- scale rated from 0 (not important) to 7 (a very great deal important).
    - Patient Global Impression of Change Impact (GROCi) (only measured at follow-up)- scale rated from 0 (not important) to 7 (a very great deal important).
    - Patient Acceptable Symptom State (PASS): "Considering all the different ways your pain symptoms are affecting you, if you were to stay in this state for the next few months, do you consider that your current state is satisfactory?" (Yes/No)
    - Grip Strength (Subjects with UE symptoms only)- Measured using a dynamometer bilaterally.
    - Leg Press 1 Repetition Maximum Test (Subjects with LE symptoms only): The subject will perform 2 warm-up sets with light resistance. Weight will be increased with the goal of finding the 1 repetition maximum weight within 4 trials. A 2-minute rest period will be given between trials.
    - Patient Specific Functional Scale: Goals are set by PT and subject. The patient rates their ability to complete the task described in to goal on a 0(unable to perform) to 10 (Able to perform activity at the same level as before injury or problem).
    - Adverse events
    - Participant disposition: Who was enrolled/reasons for exclusion, reason for dropout (if known)

<u>Interventions:</u>

- <u>rTMS:</u>
    - rTMS will be delivered using a commercially available magnetic stimulator (Rapid^2, Magstim Inc., Eden Prairie, MN) with a figure-of-8 coil at 10 Hz. With subjects in a seated position, the coil will be positioned on the scalp, contralateral to the subject's symptomatic side. Coil orientation will be optimized for stimulation of the abductor pollicis brevis.
    - Targeting:

      Subjects will wear a lycra cap so marks can be made to facilitate proper targeting. Single-pulse stimulations will be delivered over various locations of the contralateral primary motor cortex to identify the optimal location for stimulation of the target muscle. Motor evoked potentials (MEP) of the abductor pollicis brevis will be monitored using electromyography (EMG) (Motion Lab Systems Inc., Baton Rouge, LA). Once the optimal stimulation position is identified a mark will be made on the lycra cap. The motor threshold (MT) of the muscle will then be

identified by systematically adjusting the pulse intensity. The MT will be considered the lowest stimulation intensity at which 5 out of 10 MEPs have a peak-to-peak amplitude of at least 50 microvolts, measured using RMG of the abductor pollicis brevis.

- Parameters:

  rTMS will be performed at the identified optimal location at 10Hz using an intensity that is 80% of the MT. Pulse trains will be delivered for 10 seconds, with a 30 second rest for 20 repetitions. This will result in a total of 2,000 pulses of magnetic stimulation.

- Safety:

  The most common side effects during stimulation are local discomfort and headaches. Subjects will be asked to inform the researcher if they are unable to tolerate the rTMS. If they cannot tolerate the stimulation the subjects will be given two options. The first option will be to reduce the stimulation intensity to a point that is tolerable. The second option will be to stop the stimulation. If they elect to stop the stimulation the subject can decide to end participation in the study or try another session at a subsequent date. Subjects will also be monitored for EMG activity at the abductor pollicis brevis and visual twitch response at other muscles. If this activity increases over the course of the stimulation the intensity will be reduced.

- <u>Sham rTMS:</u>
  - Sham rTMS will be performed using the same coil and delivery device used in the real rTMS group. The sham group will start with the same localization procedure as the real rTMS group. The magnet will then be moved over the vertex of the skull and the intensity will be dropped to 5% of the maximal stimulation output or half of the treatment intensity (40% of MT) used in the real rTMS group, whichever is lower. Subjects in both groups will be told that after localization, the stimulation intensity will be lowered for the treatment. The sham group will be told that with this lower intensity they may experience minimal to no sensation from the stimulus. Allocation will be disclosed to all participants after the last data collection timepoint.
- <u>Rehabilitation:</u>
  - Rehabilitation will consist of education, value-based goal setting, Graded Motor Imagery (GMI) (3 components described below), meditation, and graded activity. Subjects will complete activities at treatment sessions and be asked to perform certain treatment activities at home.

- Week 1: Pain education, functional value-based goal setting, laterality training (first component of GMI), one task for graded activity (task-based on patient goals)
- Week 2: Continue week 1 activity, add graded motor imagery (second component of GMI), progress 1st graded activity, and initiate 2nd graded activity exercise.
- Week 3- Mirror therapy (third component of GMI), add meditation, assess knowledge and update education as needed, progress graded activity 1 and 2, and add 3rd graded activity if appropriate based on patient goals.
- Week 4- Continue with week 3 activities. Discuss experience with meditation and progress graded activity as tolerated.

- Pilot Testing
  - This is a new treatment protocol for our lab. To test and adjust the logistics of the protocol 1-3 subjects will be enrolled as pilot subjects. The subjects will complete the standard protocol but will not be randomized. All 1-3 subjects in the pilot testing will receive the real rTMS.

11.1 Describe what data, including long-term follow-up, will be collected.

NOTE: For studies with multiple data collection points or long-term follow up, consider including a schedule or table in your response.

Measurements:

- The first visit
  - All instruments except the GROC
  - Basic demographics and other relevant medical information will be collected at this visit
- The last visit of each week
  - All outcome instruments will be collected
- All outcome instruments will be collected at 4-time points after the termination of the interventions-via REDCap e-mail survey or mailed survey if the subject does not have access to e-mail.
  - 4 weeks
  - 3 months
  - 6 months
  - 1 year

List, and upload, any instruments or measurement tools used to collect data (e.g. survey, scripts, questionnaire, interview guide, validated instrument, data collection form).

All of the listed instruments will be uploaded with this IRB submission.

- Numeric Pain Rating Scare (0-10): Weekly average and worse and least pain intensity over past 24 hours
- NIH Patient-Reported Outcomes Measurement Information System (PROMIS): Pain interference, pain behavior, physical functioning, satisfaction with discretionary social activity, satisfaction with social roles, fatigue, depression, anxiety, and anger.
- CRPS Severity Score
- Patient Global Impression of Change (GROC) (only measured at follow-up)- scale rated from -7 (a very great deal worse) to +7 (a very great deal better) with 0 being about the same.
- Patient Acceptable Symptom State (PASS): Considering all the different ways your pain symptoms are affecting you, if you were to stay in this state for the next few months, do you consider that your current state is satisfactory?" (Yes/No)
- Adverse events
- Participant disposition: Who was enrolled/reasons for exclusion, reason for dropout (if known)

11.2 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records).

No records will be used. All data will be collected directly from the patient.

11.3 Describe whether individual subject results (such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Data will not be shared with subjects.

11.4 Indicate whether or not generalized study results will be shared with subjects or others, and if so, describe how these will be shared.

Results will not be shared with subjects unless requested.

12.0 Study Timelines

12.1 Describe the anticipated duration of the study needed to enroll all study subjects.

Study enrollment is anticipated to take 2 years. If subject numbers have not been met at 2 years, but we continue to have consistent enrollment, the study period may be extended.

12.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.

Study visits will occur over a 4-week period. Subjects will be seen for 4 visits the first week and then 2 visits a week for the remaining 3 weeks (total of 10 visits). The first visit will take approximately 2.5-3 hours and subsequent visits will be approximately 1.5 hours in duration. Subjects who fail to attend approximately 80% of the visits (miss more than 2 sessions) will be removed from the study and treatment will be stopped.

12.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).

Approximately 3.5 to 4 years. 1-2 years for study enrollment, 1-year follow-up, and up to 6 months for analyses.

13.0 Research Setting

13.1 Describe all facilities/sites/locations where you will be screening and conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.

Example: "A classroom setting in the New Academic Building equipped with a computer with relevant survey administration software", "The angiogram suite at University Hospital downtown campus", The Clinical Research Unit in the Institute for Human Performance."

Initial study screening will be conducted via telephone. Consent, initial data collection, and rTMS treatment will occur at the Motion Analysis Lab at the Institute of Human Performance. Rehabilitation sessions will be administered at the rehabilitation gym on the second floor of the Institute of Human Performance. During the 4-week treatment sessions, instruments will be completed electronically after the rehabilitation sessions on the second floor of the Institute of Human Performance. Measurements after the 4-week treatment sessions will be administered electronically.

13.2 For research procedures being conducted, for this study, external to Upstate (e.g., in schools, out-of-state, internationally, etc.) describe:

- *Site-specific regulations or customs affecting the research*
- *The composition and involvement of any community advisory board*
- *Local scientific and ethical review structure outside the organization.*
- *Local issues affecting the research and rights of research subjects.*

NOTE: This question is not referring to multi-center research. If this research is being conducted internationally, Supplemental Form E must be completed and uploaded.

☒ N/A: This study is not conducted outside of Upstate.

14.0 Resources and Qualifications

14.1 The Principal Investigator (PI) must confirm, in consultation with Chair and Dean as applicable, that adequate resources are present to conduct and complete the study compliantly and safely. Specifically:

- *The proposed subject population(s) are available in sufficient numbers to meet the study requirements*
- *Sufficient funds are available to conduct and complete the study compliantly and safely*
- *The PI and study team have sufficient time to conduct and complete the study compliantly and safely*
- *The PI has determined that the named study team is qualified to conduct the research compliantly and to monitor the safety and welfare of the enrolled research subjects effectively*
- *The PI ensures that the study team is fully aware of his/her involvement in this study and the details of the study protocol*
- *The PI ensures that the study teams will only be involved in research procedures for which they have been trained, and are currently certified and/or licensed, if required.*

☒ **Confirmed**

14.2 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the research, if applicable. (e.g, "on-call availability of a counselor or psychologist for a study that screens subjects for depression"

We do not anticipate any significant adverse events from our protocol. If psychological or medical adverse events requiring immediate medical attention occur, 911 will be called for medical management. For any non-emergency physical or psychological adverse events subjects will be referred to their primary care physician. For subjects who do not have a primary care physician they will be referred to an urgent care center or a hospital emergency room.

14.3 Describe your process to ensure that all study team members are updated on the progress of the research and the regulatory requirements (including enrolled subjects, unanticipated problems etc.)

All study members involved in treatment sessions will be trained on the protocol and emergency response plans by the PI.

15.0 Provisions to Protect the Privacy Interests of Subjects

15.1 Describe how you will protect subjects' privacy interests during the course of the research and any steps you will take to make the subject feel at ease.

NOTE: Privacy refers to an individual's desire/right to control access to or to place limits on whom they interact with or whom they provide personal information. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.

Examples of appropriate responses include: "participant only meets with a study coordinator in a private office setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

Data collection and treatment will be performed in a private research or clinical setting at the Institute of Human Performance on Upstate's campus. Subjects will have the right to refuse to answer any question that they do not feel comfortable answering.

16.0 Confidentiality

A. Confidentiality/Security of Study Data

Describe the local procedures for maintenance of security and confidentiality of **study data and any records that will be reviewed for data collection.**

16.1 Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, certificates of confidentiality, and separation of identifiers and data, as applicable. Include physical (e.g. paper) and electronic files.

Personal-identifying information will be collected using Upstate's REDCap system. Any downloaded personal-identifying information will be kept on the PIs password protected office PC, located in his locked private office in the New Academic Building. Any documents containing personal identifying information will be kept in a locked cabinet located in a secure room on campus (either the PIs office or in the Motion Analysis Lab). Once data collection is completed all personal-identifying information will be removed from the dataset by the PI. Only de-identified data will be shared with other research members or used for publication/dissemination.

16.2 How long will the data be stored?

When study activities are completed, the data will be archived in REDCap, and stored on the PI's password protected computer in his private office (RM 3340 New Academic Building) for up to seven years.

16.3 Who will have access to the data?

Only study personnel included on this IRB application.

16.4 Who is responsible for receipt or transmission of the data?

The principal investigator will be responsible for receipt or transmission of the data.

16.5 How will the data be transported/transmitted?

Any physical paper documentation will be transported by study personal in sealed envelopes between testing/treatment areas and storage areas. Electronic data will be transmitted between study personnel using Upstate email or OneDrive/Dropbox sharing feature.

B. Confidentiality of Study Specimens

Describe the local procedures for maintenance of confidentiality of study specimens.

☒ **N/A:** No specimens will be collected or analyzed in this research.
(Skip to Section 17.0)

16.6 Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.

N/A

16.7 How long will the specimens be stored?

N/A

16.8 Who will have access to the specimens?

N/A

16.9 Who is responsible for receipt or transmission of the specimens?

N/A

16.10 How will the specimens be transported?

N/A

17.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

☐ **N/A:** This study is not enrolling subjects OR is limited to records review procedures only OR is a minimal risk study

17.1 Describe the plan to evaluate the data periodically regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

Subjects will be directly monitored by study personnel during the rTMS and rehabilitation sessions. During rTMS it is expected that some subjects may experience mild headaches, local scalp discomfort, and muscle twitching. Subjects will be consistently monitored and stimulation intensity will be reduced if symptoms are not tolerated or if muscle twitch magnification occurs. During rehabilitation sessions, it is expected that some subjects may experience temporary exacerbation of their normal symptoms. The physical therapist delivering care will monitor subjects and adjust treatment intensity based on the subject's tolerance. Subjects can also request to stop participation in the study at any time for any reason. Study personnel will be in close communication and if the protocol is consistently poorly tolerated by subjects the study will be paused and the protocol will be reviewed and changed as needed.

17.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

EMG data and visual observation will be used to assess muscle activation during rTMS. Subject report will be used during rTMS and rehabilitation to monitor response.

17.3 Describe any primary or secondary safety endpoints.

Muscle activity spreading beyond the stimulated area or increasing in magnitude despite lowering stimulation intensity. Unpleasant sensation associated with the interventions that is deemed intolerable or excessive by the subject or research personnel.

17.4 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants)

Muscle activation will be recorded via EMG. At the end and beginning (other than the first session) of every rTMS and rehabilitation session subjects will be asked to report any adverse events. This will be recorded on REDCap as either "none" or, if present, the symptoms will be documented.

17.5 Describe the frequency of safety data collection, including when safety data collection starts.

Safety data will be collected at every treatment session. This will occur before (to assess response to previous sessions), during, and after each treatment session.

17.6 Describe who will review the safety data.

The primary investigator and any study personnel involved in treatment delivery. If these individuals have concerns, they will discuss the safety data with the entire research team.

17.7 Describe the frequency of review of cumulative safety data.

Normal and expected mild adverse events will be dealt with by the treating provider and reported to the PI, as they occur. All events requiring subjects to stop a treatment will be discussed with the entire research team. The study team will have meetings at least every 3 months to discuss any safety concerns.

17.8 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Not applicable. Safety data will be monitored onsite by investigators.

17.9 Describe any conditions that trigger an immediate suspension of the research.

A seizure occurring in one of the participants.

18.0 Withdrawal of Subjects

☐ N/A: This study is not enrolling subjects. This section does not apply.

18.1 Describe anticipated circumstances under which subjects may be withdrawn from the research without their consent.

If a subject misses more than 3 treatment sessions, or if they have adverse events deemed unacceptable by an investigator.

18.2 Describe any procedures for orderly termination.

NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Subjects who miss an appointment will be contacted via telephone (and email if needed). If possible, they will be allowed to make up the missed session. If they are withdrawn from the study without consent, they will be contacted via phone. If phone contact cannot be made, an e-mail informing them of the withdrawal and the reason will be sent by the PI.

18.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

Demographic information and the reason for withdrawal (if known) will be reported for all subjects who enroll in the study. Subjects who withdraw from the treatment will be allowed to continue with the self-reported data collection, however, only data from those who complete 80% of the treatment will be included in the primary analysis. Subjects who officially withdraw or are lost to follow-up after finishing the treatment sessions will be included in the analysis, as appropriate. For example, subjects who complete the 3-month follow-up, but not the 6 month or 1-year follow-up will be included in the 3-month analysis. Data collected for subjects who withdraw will be secured and retained in the same way as subjects who do not withdraw.

18.4 Describe what will happen to data already collected.

Data collected for subjects who withdraw will be secured and retained in the same way as subjects who do not withdraw.

19.0 Risks to Subjects

19.1 In your opinion, what is the overall risk (physical and nonphysical) to research subjects in this study (minimal, greater than minimal or unknown)

The risks of this study are minimal.

Repetitive Transcranial Magnetic Stimulation (rTMS) is delivered using a Class II FDA device that is approved for the treatment of depression. The device is currently being investigated for use in other disorders, including headaches, Obsessive-Compulsive Disorder, and as a method to treat pain. There have been three review articles written on the safe clinical use of rTMS. [1–3] The most recent article was published in 2021 and classified the risks of rTMS as "very low".[2] The most common side effects of rTMS are headaches and local pain around the stimulation site. These side effects are transient and usually mild.[1] The most concerning potential adverse event is the induction of a seizure. There have been 41 reported cases of seizures that may have been induced by rTMS.[2,4] The majority of these seizures occurred before the publication of the 1998 safety guidelines.[2,3] Thirteen of the seizures occurred in healthy individuals and 28 occurred in patients with a psychiatric or neurologic condition. Fifty four percent of the reported seizures were classified as general and 27% were focal to bilateral tonic-clonic.[4]

The overall risk of seizure with rTMS is difficult to calculate because the number of total exposures is unclear. Lerner et. al surveyed 174 laboratories and clinics that utilize rTMS in research or in clinical care.[5] The respondents reported 24 seizures over an estimated 318,560 TMS sessions (.08/1000). TMS sessions that followed the parameters described in the 2009 guidelines[1] and included only low risk patients resulted in a seizure risk of <.02/1000 sessions (1 seizure per 60,000 sessions). Subjects with elevated seizure risk treated with rTMS following the guidelines had a .33/1000 risk of seizure.

Several factors that have the potential to increase the risk of seizures with rTMS have been identified. Due to the very low incidents of seizures, it is difficult to confidently know if and how much these factors increase the risk of seizure. Authors have also errored on the side of overestimation by setting a low bar for associating TMS with the seizure.[2,5] It is likely that several of the reported seizures were convulsive syncopal episodes or seizures that were unrelated to the TMS. One of the most accepted risk factors for TMS induced seizure is a history of epilepsy.[2] In the Lerner study, 29% (7/24) of the seizure cases were in patients with a history of epilepsy. Cases of seizure also occurred in individuals with a history of stroke (5), psychiatric disorders treated with medications that lower the seizure threshold (3), tumors (2), and arteriovenous malformation (1).[5] Four seizures (17%) occurred in individuals without any identifiable risk factors.[5] Although seizure is a serious risk factor, there have been no reports of long-term deleterious effects in those individuals who had a seizure that was attributed to rTMS.

Based on this information we agree with Rossi et al that treatment with a Transcranial Magnetic Stimulator is low risk.[1] To further reduce the risk of adverse events we will follow the accepted stimulation and monitoring guidelines.[2,6] Stimulation parameters will be at intensities below motor evoked potential, we will provide adequate time between stimulation trains, and we will monitor for increasing EMG activity in contralateral muscles.[6] We will exclude subjects who are epileptic and who have implanted metal or electronic devices in or near their head, such as aneurism clips, stents, pacemakers, cochlear implants, implanted brain stimulators, and ocular implants. The research team will have an emergency plan in place to deal with any adverse events. Subjects receiving rTMS will be placed in a safe position that will reduce the risk of

injury if a seizure occurs. If a serious adverse event, such as a seizure occurs, the research team will call EMS services and encourage the subject to seek immediate emergency care. Subjects will be made aware of the potential adverse events during the informed consent process.

1. Rossi S, Hallett M, Rossini PM, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009;120(12):2008-2039. doi:10.1016/j.clinph.2009.08.016
2. Rossi S, Antal A, Bestmann S, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin Neurophysiol*. 2021;132(1):269-306. doi:10.1016/J.CLINPH.2020.10.003
3. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalogr Clin Neurophysiol*. 1998;108(1):1-16. doi:10.1016/S0168-5597(97)00096-8
4. Chou Y hui, Ton That V, Chen AYC, Sundman M, Huang YZ. TMS-induced seizure cases stratified by population, stimulation protocol, and stimulation site: A systematic literature search. *Clin Neurophysiol*. 2020;131(5):1019-1020. doi:10.1016/J.CLINPH.2020.02.008
5. Lerner AJ, Wassermann EM, Tamir DI. Seizures from transcranial magnetic stimulation 2012–2016: Results of a survey of active laboratories and clinics. *Clin Neurophysiol*. 2019;130(8):1409-1416. doi:10.1016/J.CLINPH.2019.03.016
6. Repetitive Transcranial Magnetic Stimulation (rTMS) Systems - Class II Special Controls Guidance for Industry and FDA Staff | FDA. US Food and Drug Administration Guidance Documents. Published 2011. Accessed November 23, 2021. https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/repetitive-transcranial-magnetic-stimulation-rtms-systems-class-ii-special-controls-guidance

19.2 Describe if any subjects are withdrawn from therapeutic procedures or drugs (e.g., washout periods) prior to, or during, their participation in the study.

Subjects will not be asked to stop any therapeutic procedure or drug. Subjects who have recently initiated a new intervention will be asked to wait 2 months before starting the study interventions. Subjects currently attending rehabilitation will be asked to wait 3-2 months from the last session before starting the study interventions. Subjects will be asked to not start any new

interventions during the 4 week intervention period of the trial. The follow-up data collection survey will ask participants to report any changes or additions to their management strategies.

19.3 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.

NOTE: Breach of confidentiality is always a risk for identifiable subject data.

There have been three review articles written on the safe clinical use of rTMS. [1–3] The most recent article was published in 2021 and classified the risks of rTMS as "very low".[2] The most common side effects of rTMS are headaches and local pain around the stimulation site. These side effects are transient and usually mild.[1] The most concerning potential adverse event is the induction of a seizure. There have been 41 reported cases of seizures that may have been induced by rTMS over the past three decades since the introduction of rTMS.[2,4] The majority of these seizures occurred before the publication of the 1998 safety guidelines.[2,3] Thirteen of the seizures occurred in healthy individuals and 28 occurred in patients with a psychiatric or neurologic condition. Fifty-four percent of the reported seizures were classified as general and 27% were focal to bilateral tonic-clonic.[4]

The overall risk of seizure with rTMS is difficult to calculate because the number of total exposures is unclear. Lerner et. al surveyed 174 laboratories and clinics that utilize rTMS in research or in clinical care.[5] The respondents reported 24 seizures over an estimated 318,560 TMS sessions (.08/1000). TMS sessions that followed the parameters described in the 2009 guidelines[1] and included only low risk patients resulted in a seizure risk of <.02/1000 sessions (1 seizure per 60,000 sessions). Subjects with elevated seizure risk treated with rTMS following the guidelines had a .33/1000 risk of seizure.

Several factors that have the potential to increase the risk of seizures with rTMS have been identified. Due to the very low incidents of seizures, it is difficult to confidently know if and how these factors increase the risk of seizure. Authors have also errored on the side of overestimation by setting a low bar for associating TMS with a seizure.[2,5] Several of the reported seizures were likely convulsive syncopal episodes or seizures that were unrelated to the TMS. One of the most accepted risk factors for TMS induced seizure is a history of epilepsy.[2] In the Lerner study, 29% (7/24) of the seizure cases were in patients with a history of epilepsy. Cases of seizure also occurred in individuals with a history of stroke (5), psychiatric disorders treated with medications that lower the seizure threshold (3), tumors (2), and arteriovenous malformation (1).[5] Four seizures (17%) occurred in individuals without any identifiable risk factors.[5] Although seizure is a serious risk factor, there have been no reports of long-term deleterious effects in those individuals who had a seizure that was attributed to TMS.

Based on this information we agree with Rossi et al that treatment with a Transcranial Magnetic Stimulator is low risk.[1] To further reduce the risk of adverse events we will follow the accepted stimulation and monitoring guidelines.[2,6] Stimulation parameters will be at intensities below motor evoked potential, we will provide adequate time between stimulation trains, and we will monitor for increasing EMG activity in contralateral muscles.[6] We will also exclude subjects who are epileptic, with a family history of epilepsy in immediate blood relatives, pregnant, and

who have implanted metal or electronic devices in or near their head, such as aneurism clips, stents, pacemakers, cochlear implants, implanted brain stimulators, and ocular implants. The research team will have an emergency plan in place to deal with any adverse events. Subjects receiving rTMS will be placed in a safe position that will reduce the risk of injury if a seizure occurs. If a serious adverse event, such as a seizure occurs, the research team will call EMS services and encourage the subject to seek immediate emergency care. Subjects will be made aware of the potential adverse events during the informed consent process.

No significant adverse events have been reported for the rehabilitation procedures that will be used in this study. The procedures will be administered by licensed physical therapists with experience treating patients with CRPS. The procedures used during the rehabilitation sessions is standardized but will be tailored to the individual subject's tolerance.

Subjects will also be informed that study personnel will not be responsible for the medical costs incurred as a result of an adverse event.

1. Rossi S, Hallett M, Rossini PM, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009;120(12):2008-2039. doi:10.1016/j.clinph.2009.08.016
2. Rossi S, Antal A, Bestmann S, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin Neurophysiol*. 2021;132(1):269-306. doi:10.1016/J.CLINPH.2020.10.003
3. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalogr Clin Neurophysiol*. 1998;108(1):1-16. doi:10.1016/S0168-5597(97)00096-8
4. Chou Y hui, Ton That V, Chen AYC, Sundman M, Huang YZ. TMS-induced seizure cases stratified by population, stimulation protocol, and stimulation site: A systematic literature search. *Clin Neurophysiol*. 2020;131(5):1019-1020. doi:10.1016/J.CLINPH.2020.02.008
5. Lerner AJ, Wassermann EM, Tamir DI. Seizures from transcranial magnetic stimulation 2012–2016: Results of a survey of active laboratories and clinics. *Clin Neurophysiol*. 2019;130(8):1409-1416. doi:10.1016/J.CLINPH.2019.03.016
6. Repetitive Transcranial Magnetic Stimulation (rTMS) Systems - Class II Special Controls Guidance for Industry and FDA Staff | FDA. US Food and Drug Administration Guidance Documents. Published 2011. Accessed November 23, 2021. https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/repetitive-transcranial-magnetic-stimulation-rtms-systems-class-ii-special-controls-guidance

19.4 Describe procedures performed to minimize the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.

Subjects will be screened for risk factors that may increase the chances of an adverse event using a standard form. The treatment protocols and inclusion/exclusion criterion have been developed based on the most up-to-date safety guidelines. Safety and monitoring procedures, as described above, will be implemented at all times during the treatment sessions.

19.5 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

N/A

19.6 Indicate which research procedures, if any, may have risks to an embryo or fetus should the subject be or become pregnant.

☒ **N/A**

19.7 If you responded to 19.6 that there are such risks, how will you minimize the risk of a pregnancy occurring during the course of the study? (Select all that apply)

- ☐ Counseling on birth control and /or abstinence
- ☐ Pregnancy test during the study
- ☐ Pregnancy test prior to initiation of the study
- ☐ Other _____
- ☒ **N/A**

19.8 If applicable, describe possible risks to others who are not subjects.

N/A

20.0 Potential Benefits to Subjects

20.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits.

Based on the current literature it is expected that the rTMS and rehabilitation procedures used in this study will result in benefits such as reduced pain and increased function.[1–4] Subjects in the sham group will still receive high-quality rehabilitation that could lead to improved symptoms.

1. Picarelli H, Teixeira MJ, De Andrade DC, et al. Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. *J pain*. 2010;11(11):1203-1210. doi:10.1016/J.JPAIN.2010.02.006
2. Gaertner M, Kong JT, Scherrer KH, Foote A, Mackey S, Johnson KA. Advancing Transcranial Magnetic Stimulation Methods for Complex Regional Pain Syndrome: An Open-Label Study of Paired Theta Burst and High-Frequency Stimulation. *Neuromodulation*. 2018;21(4):409-416. doi:10.1111/NER.12760
3. Pleger B, Janssen F, Schwenkreis P, Völker B, Maier C, Tegenthoff M. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. *Neurosci Lett*. 2004;356(2):87-90. doi:10.1016/J.NEULET.2003.11.037
4. Moseley GL. Graded motor imagery for pathologic pain: A randomized controlled trial. *Neurology*. 2006;67(12):2129-2134. doi:10.1212/01.wnl.0000249112.56935.32

20.2 Indicate if there is no direct benefit.
NOTE: Compensation cannot be stated as a benefit.

N/A

Indicate if there is a potential benefit to others, future science or society.

N/A

21.0 Compensation for Research-Related Injury

☒ **N/A:** The research procedures for this study do not present risk of research-related injury. This section does not apply.

21.1 If the research procedures carry a risk of research related injury, describe the available compensation to subjects in the event that such injury should occur.

22.0 Economic Burden to Subjects

22.1 Describe any costs that subjects may be responsible for because of participation in the research.
NOTE: Some examples include transportation or parking.

Subjects may be responsible for transportation, parking, and the recognize application (used for laterality training, 6$).

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

23.0 Compensation for Participation

☒ **N/A:** There is no compensation for participation. This section does not apply.

23.1 Describe the amount/nature and timing/scheduling of any compensation to subjects, including monetary, course credit, or gift card compensation. Describe any prorated payments based on participation.

24.0 Informed Consent

24.1 Will you be obtaining consent from subjects?

☒ ***Yes*** *(If yes, Provide responses to each question in this Section, and upload your consent documents)*

☐ ***No*** *(If no, Skip to next section)*

24.2 Describe how the capacity to consent will be assessed for all subjects. (See SOPs, section 14.7.2 for guidance)

The capacity to consent will be assessed during the screening process for all subjects. Subjects will be asked if they have any questions or difficulty understanding the verbal and written communication, and the associated risks of the procedures. If comprehension difficulties are present, further verbal communication will be offered (including reading the consent documents to the subject) by an investigator. Individuals who are not fluent in English will be excluded from the study.

24.3 Describe the consent process that will be conducted to ensure that subject is fully informed regarding study details and subject rights. Include where the consent process will take place, with consideration of the need to protect the subject's right to privacy.

Step 1: During the phone screening process subjects will be asked if they would like a copy of the consent documents e-mailed to them before the first visit. This will be encouraged so subjects have ample time to review the documents. Study procedures will be verbally explained to subjects using a standardized script. Subjects will be encouraged to ask questions about the study. Subjects in the pilot phase will receive a consent document that does not include information about randomization and sham rTMS. The consent document provided to subjects in

the randomized phase of the trial will contain language on the randomization process, sham rTMS, and blinding.

Step 2: During in-person screening study procedures will be verbally explained to subjects using a standardized script. Subjects will be encouraged to ask questions about the study.

Step 3: During the in-person screening potential subjects will be given 2 paper copies of the consent documents. They will be given as much time as needed to review the documents and ask questions. Subjects who agree to participate will keep one copy of the consent documents and provide a signed copy to the investigator.

24.4 Describe the process to ensure that subjects are provided with sufficient time to consider taking part in the research study. Include whether there is any time period expected between informing the prospective subject and obtaining the consent.

NOTE: It is respectful to the prospective subject to ensure that sufficient time is given to have their questions answered and to consider their participation

When possible, an e-mail version of the consent documents will be sent after the phone screening. At the in-person meeting, subjects will be given a semi-private location (away from the investigator) to review the documents. They will be asked to return to the testing area when they are finished reviewing the documents or if they have any questions. Subjects who are hesitant to consent will be given the option to take the documents home and reschedule for another day if they decide to participate.

24.5 Describe the process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.

At the start of the study, subjects will be informed that they can drop out at any time. During the sessions study, personnel will monitor subjects for adverse physical or psychological responses. Subjects who express concern about the study or demonstrate adverse physical responses will be reminded that they can drop out of the study at any time.

Non-English Speaking Subjects

☒ *N/A: This study will not enroll Non-English speaking subjects.*

24.6 Indicate which language(s) other than English are likely to be spoken/understood by the prospective study population or their legally authorized representatives.

N/A

24.7 If subjects who do not speak English will be enrolled, describe the process to consent the subjects, as well as the process to be used to ensure their understanding of research procedures throughout the conduct of the study. Review SOP's section 13.9.1 for important policies in this regard.

N/A

Adults Unable to Consent

☒ **N/A:** This study will not enroll adults unable to consent (go to next section).

24.8 Justify why it is necessary to include adult subjects who are unable to consent.

N/A

24.9 Describe how you will identify Legally Authorized Representatives (LAR) for the subjects that will be consistent with the NYS law (Review SOP's section 13.3)

Note: For research conducted outside of New York State, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the research.

N/A

24.10 Describe the process for obtaining assent from the adult subjects
Indicate whether assent will be obtained from all, some, or none of the subjects. If some, indicate which adults will be required to assent and which will not.

N/A

If assent will not be obtained from some or all subjects, provide an explanation of why not.

N/A

24.11 Describe whether assent of the adult subjects will be documented and the process to document assent.

N/A

24.12 Describe how you will obtain consent from a subject to use their data if they later become capable of consent. How will capacity to consent be assessed and by whom?

N/A

25.0 Waiver or Alteration of Consent Process

Complete this section if:

- Informed consent will not be obtained at all
- Informed consent will be obtained, but not documented, or
- consent will be obtained, but not all required information will be disclosed (e.g., in deception research)

☒ **N/A:** A waiver or alteration of consent is not being requested.

25.1 Review, complete, and upload Supplemental Form F: General Waiver or Alteration of Consent

☐ Confirmed

26.2 If the research involves a waiver of the consent process for planned emergency research, please contact the IRB Office for guidance regarding assistance in complying with federal regulations governing this activity (see SOPs section 13.12).

26.0 Multi-Site Research (Multisite/Multicenter Only)

☒ **N/A:** This study is not an investigator-initiated, multi-site study. This section does not apply.

26.1 If this is a multi-site study where Upstate is the lead site and/or the IRB of record, describe the processes to ensure communication among sites. Include:

- *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

26.2 Describe the method for communicating to engaged participating sites:

- *Problems*
- *Interim results*
- *Study closure*

*26.3 Indicate and statistically justify the total number of subjects that will be enrolled or records that will be reviewed **across all sites**.*

27.0 Banking Data or Specimens for Future Unspecified Use

☒ **N/A:** This study is not storing data or specimens for research outside the scope of the present protocol. This section does not apply.

27.1 If data will be banked (stored) for research outside of the scope of the present protocol, describe where the data will be stored, how long they will be stored, how will they be accessed, and who will have access to the data

NOTE: The response here must be consistent with the information provided to subjects in the Consent Documents

27.2 If specimens will be banked (stored) for research outside of the scope of the present protocol, describe where the specimens will be stored, how long they will be stored, identifiers that will be associated with each specimen, how will they be accessed, and who will have access to the specimens

NOTE: The response here must be consistent with the information provided to subjects in the Consent Documents

27.3 Describe the procedures to release banked data and/or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

28.0 Drugs and Devices

☐ **N/A:** This study does not involve drugs or devices. This section does not apply.

28.1 Does this study involve use of radiopharmaceuticals? ☐ Yes ☒ No

28.2 For investigational devices (including marketed devices being used off label & humanitarian use devices), Provide the following information:

- *Where will the device(s) be stored? Note that the storage area must be within an area under the PI's control*
- *Describe the security of the storage unit/facility*
- *Provide full detail regarding how the dispensing of the device(s) will be controlled (accountability of removal/return of used devices, and disposition of remaining devices at the conclusion of the investigation) and documented (accounting records/logs)*

The device is stored in the Motion Analysis Lab at the Institute for Human Performance on the SUNY Upstate campus. The lab is private with key card access only. The use of the device will be documented in REDCap for each subject.

28.3 For research including drugs (investigational and FDA approved). Complete and upload the Pharmacy Worksheet and supporting materials (IB's) and obtain Pharmacy approval and sign off.

☐ Confirmed

☒ **N/A:** This study does not involve drugs