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# Brivaracetam to Reduce Neuropathic Pain in Chronic SCI: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial:

# Protocol and Statistical Analysis Plan Cover Page

**ClinicalTrials.gov ID** NCT05639946

**Date** April 15, 2024

**ANCILLARY REVIEWS**

**DO NOT DELETE. Submit the completed checklist below with your protocol.**

| **Which ancillary reviews do I need and when do I need them?** Refer to HRP-309 for more information about these ancillary reviews. | | | |
|---|---|---|---|
| **Select yes or no** | **Does your study…** | *If yes…* | ***Impact on IRB Review*** |
| ☐ **Yes** ☒ **No** | Include Gillette resources, staff or locations | *Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com* | **Required prior to IRB submission** |
| ☒ **Yes** ☐ **No** | Involve Epic, or Fairview patients, staff, locations, or resources? | *The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org | **Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.** |
| ☒ **Yes** ☐ **No** | Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection? | *The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu* *See: https://policy.umn.edu/research/indide* | |
| ☒ **Yes** ☐ **No** | Require Scientific Review? Not sure? See guidance in the Investigator Manual (HRP-103). | *Documentation of scientific merit must be provided. Contact: hrpp@umn.edu* | |

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|---|---|---|---|
| ☐ **Yes**<br>☒ **No** | Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco? | *Complete the CPRC application process. Contact: ccprc@umn.edu* | |
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| ☒ **Yes**<br>☐ **No** | Use the Center for Magnetic Resonance Research (CMRR) as a study location? | *Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu* | |
| ☐ **Yes**<br>☒ **No** | Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents? | *Complete the IBC application via eprotocol.umn.edu* | |
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| ☐ **Yes**<br>☒ **No** | Use data from the Information Exchange (IE)? | *The Information Exchange ancillary review will be assigned to your study by IRB staff* | **Approval must be received prior to IRB approval.** |

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| | | *Contact: ics@umn.edu* | **These groups do not have a separate application process but additional information from the study team may be required.** |
| ☐ **Yes**<br>☒ **No** | Use the Biorepository and Laboratory Services to collect tissue for research? | *The BLS ancillary review will be assigned to your study by IRB staff. Contact: Jenny Pham Pham0435@umn.edu* | |
| ☐ **Yes**<br>☒ **No** | Have a PI or study team member with a conflict of interest? | *The CoI ancillary review will be assigned to your study by IRB staff Contact: becca002@umn.edu* | |
| ☒ **Yes**<br>☐ **No** | Need to be registered on clinicaltrials.gov? | *If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff Contact: kmmccorm@umn.edu* | |
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**PROTOCOL COVER PAGE**

| | |
|---|---|
| **Protocol Title** | Brivaracetam to Reduce Neuropathic Pain in Chronic SCI: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial |
| **Principal Investigator/Faculty Advisor** | Name: Ricardo Battaglino, PhD |
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| **IND/IDE # (if applicable)** | 150388 |
| **IND/IDE Holder** | Leslie Morse, DO |
| **Investigational Drug Services # (if applicable)** | NA |
| **Version Number/Date:** | Version: v7.0 APR2024 |

**REVISION HISTORY**

| Revision # | Version Date | Summary of Changes | Consent Change? |
|---|---|---|---|
| 1.1 | MAY2022 | Addressing pre-review comments | Yes |
| 2.0 | SEP2022 | Fixed typos, added language about analysis of genomic sequencing, clarified compensation; added follow-up questionnaires | Yes |
| 3.0 | NOV2022 | Enrollment numbers | Yes |
| 4.0 | APR2023 | Study duration; add bowel and bladder items; add PCL-5 and ACE-Q | Yes |
| 4.1 | | Addressed reviewer comments: changed ramp-down to 2 weeks. | |
| 5.0 | OCT2023 | Exclude vent dependent, increase drug timeline in cases of illness or other unexpected events, increase time between labs and baseline to 6-weeks to reduce participant burden | No |
| 6.0 | MAR2024 | Changing Leslie to a University of Miami collaborator, adding David Balsar, fixing typo in Pain Diary, adding disclaimer to ICF that participant may have difficulty swallowing the pill due to its size | Yes |
| 7.0 | APR2024 | Per QA audit: Removing all mention of multisite study, adding unblinding language | Yes |

**Table of Contents**

**ABBREVIATIONS/DEFINITIONS**

| | |
|---|---|
| ACC | Anterior Cingulate Cortex |
| ACGME | Accreditation Council for Graduate Medical Education |
| ACIPAC | Advanced Computational Image Processing and Analysis Center |
| AHC-IS | Academic Health Center's Information System |
| AI | Artificial Intelligence |
| ALFF | Amplitude of Low Frequency Fluctuations |
| ALT | Alanine Transaminase |
| ANOVA | Analysis of Variance |
| ART | Artifact Detection Tools |
| AST | Aspartate Transaminase |
| BID | Bis in die (Twice a Day) |
| BOLD | (SIGNAL OF ALFF) |
| BPI | Modified Brief Pain Inventory |
| BUN | Blood Urine Analysis |
| CDE | Common Data Elements |
| CHART-SF | Craig Handicap Assessment and Reporting Technique |
| CMRR | Center for Magnetic Resonance Research |
| CNS | Central Nervous System |
| Ct | Cycle threshold |
| CT | Computed Tomography |
| CTSI | Clinical and Translational Science Institute |
| DREZ | Dorsal Root Entry Zone |
| DWI | Diffusion Weighted Imaging |
| EPI | Echo-Planar Imaging |
| ERIS | Enterprise Research Infrastructure and Systems |
| FDA | Food and Drug Administration |
| FDR | False Discovery Rate |
| fMRI | functional Magnetic Resonance Imaging |
| GFR | Glomerular Filtration Rate |
| hCG | human Chronic Gonadotropin |
| HCP | Health Care Professional |
| HIPAA | Health Insurance Portability and Accountability Act |
| HPC | High Performance Computing |
| Hz | Hertz |
| ICA | ICA-Based denoising |
| IMMPACT | Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials |

| | |
|---|---|
| IND | Investigational New Drug Application |
| INR | International Normalized Ratio |
| IPA | Ingenuity Pathway Analysis |
| IQRs | Interquartile Ranges |
| IRB | Institutional Review Board |
| iv | intravenous |
| LDAP | Lightweight Directory Access Protocol |
| MEMPRAGE | Multi Echo Magnetization Prepared Rapid Acquisition Gradient Echo |
| mg | milligrams |
| MGH | Massachusetts General Hospital |
| MI | Motor Imagery |
| miR-485 | microRNA 485 |
| miRNA | MicroRNA |
| MIT | Massachusetts Institute of Technology |
| mm | millimeters |
| MNI | Montreal Neurological Institute |
| MPRAGE | Magnetization-Prepared Rapid Gradient-Echo |
| MRI | Magnetic Resonance Imaging |
| N/A | Not Applicable |
| NIDRR | National Institute on Disability, Independent Living, and Rehabilitation Research |
| NIH | National Institutes of Health |
| PACS | Picture Archive and Communication System |
| PCP | Primary Care Provider |
| PET | Positron Emission Tomography |
| pFDR | positive False Discovery Rate |
| PHQ-9 | Patient Health Questionnaire-9 |
| PHS | Partners Healthcare System |
| PI | Principal Investigator |
| PMR | Physical and Medicine Rehabilitation |
| PNS | Peripheral Nervous System |
| PRO | Patient Representative Organizations |
| RC | Research Information Services and Communications |
| REDCap | Research Electronic Data Capture |
| RNA | Ribonucleic Acid |
| RNAse | Ribonuclease |
| ROI | Region-of-Interest |
| rsfMRI | resting state functional Magnetic Resonance Imaging |

| | |
|---|---|
| SCI | Spinal Cord Injury |
| SDs | Standard Deviations |
| SG | Substantia Gelatinosa |
| Spm12 | Statistical Parametric Mapping-12 |
| SPM12 | Statistical Parametric Mapping |
| SV2A | Synaptic Vesicle Protein 2A |
| SWLS | Satisfaction with Life Scale |
| T | Tesla |
| TID | Three times a day |
| TR | Repetition Time |
| VA | Veterans Affairs |
| VAS | Visual Analog Scale |
| VPN | Virtual Private Network |

# 1.0 Objectives

*1.1* Purpose:

Spinal cord injury (SCI) is associated with severe neuropathic pain that is often refractory to pharmacological intervention. Our preliminary data suggest brivaracetam is a mechanism-based pharmacological intervention for neuropathic pain in SCI. Based on our data and other reports in the literature, we hypothesize that SCI-related neuropathic pain occurs largely because of upregulation of synaptic vesicle protein 2A (SV2A) within the substantia gelatinosa of the injured spinal cord. We further hypothesize that, compared to placebo, brivaracetam treatment reduces severe below-level SCI neuropathic pain and increases parietal operculum (parts OP1/OP4) connectivity strength measured by resting-state functional Magnetic Resonance Imaging (rsfMRI). We also hypothesize that circulating miRNA-485 levels may be associated with change in pain intensity due to brivaracetam treatment. To test these hypotheses, we will conduct a randomized, double-blind, placebo-controlled clinical trial to determine the efficacy of brivaracetam treatment for SCI-related neuropathic pain. We therefore propose the following:

<u>Specific Aims:</u>

**Specific Aim 1: Determine whether a 7-week course of daily brivaracetam reduces below-level neuropathic pain in SCI.** The objective of this aim is to assess efficacy of a 7-week course of brivaracetam to reduce neuropathic pain in men and women with SCI. We will assess change in pain intensity and related outcomes, including mood, satisfaction with life, and community integration. We will monitor drug adverse events and tolerability.

**Specific Aim 2: Determine whether a 7-week course of daily brivaracetam increases parietal operculum brain connectivity.** The objective of this exploratory aim is to assess the effect of a 7-week course of brivaracetam treatment on parietal operculum activation and connectivity in SCI. We will assess changes in cortical activity of related pain perception regions and networks in the brain in response to brivaracetam treatment compared to placebo using rsfMRI and pain-related task-based fMRI. To achieve this aim, we will test the working hypothesis that brivaracetam increases parietal operculum activation and connectivity compared to placebo, using rsfMRI, task-based fMRI, and a validated image processing protocol. We will also examine changes in network connectivity and brain activity in the insula, because of its concurrent reported importance for neuropathic pain in SCI. We will assess the association between functional connectivity of the parietal operculum and the insula and change in pain intensity in response to brivaracetam treatment.

**Specific Aim 3: Determine whether baseline microRNA-485 levels are associated with response to brivaracetam treatment.** The objective of this exploratory aim is to assess microRNA expression as a potential predictive biomarker of response to brivaracetam treatment. To achieve this, we will test the working hypothesis that baseline circulating miR-485 levels predict change in pain intensity in response to brivaracetam treatment. To test this, we will use Next-Generation sequencing. We will assess miR-485 levels at baseline and after a three-month treatment course.

## 2.0 Background

*2.1* Significance of Research Question/Purpose:

There is currently no effective pharmacological treatment for severe neuropathic pain in SCI. Identification of an oral medication that is effective, safe, and well tolerated would represent a major improvement in the clinical approach to neuropathic pain in SCI. Additionally, there are no validated predictive biomarkers of response to pharmacological therapy in neuropathic pain after SCI. This work is innovative as it seeks to develop a new, mechanism-based pharmacological intervention for neuropathic pain in SCI. Additionally, this project seeks to identify novel biomarkers of neuropathic pain and response to therapy. Development of a reliable, easy to measure biomarker that distinguishes responders from non-responders would dramatically improve clinical care for this condition. Successful completion of this work will rapidly lead to larger clinical trials testing drug efficacy and validating novel predictive biomarkers of treatment response.

*2.2* Preliminary Data:

SCI is associated with a high prevalence of severe below-level neuropathic pain that is often refractory to therapeutic interventions. Our preliminary work demonstrates overexpression of the synaptic vesicle protein 2A (SV2A) in electrically hyperactive substantia gelatinosa surgical samples in patients with neuropathic pain. The FDA-approved antiepileptic drug brivaracetam targets and binds to the SV2A protein with greater binding affinity than other drugs targeting SV2A. We have used brivaracetam off-label for compassionate reasons in severe, refractory neuropathic pain with sustained pain relief. We have identified multiple brain networks altered in SCI and modulated by neuropathic pain. Neuropathic pain also increases local brain activity of the periaqueductal gray. miR-485 regulates presynaptic expression of SV2A as well as dendritic spine density and synapse morphology and function. Therefore, circulating miR-485 may be a mechanism-based predictive biomarker of response to therapies targeting the SV2A protein, including brivaracetam. These findings, paired with our

preliminary data, suggest that reduced levels of miR-485 may contribute to the pathophysiology of SCI-induced neuropathic pain by disrupting normal levels of SV2A and neural network activity in nocioceptive neurons. Collectively, these findings provide the scientific rationale for the following hypotheses to be tested in this pilot clinical trial: compared to placebo, treatment with brivaracetam reduces severe below-level SCI neuropathic pain (Aim 1). We also hypothesize that either parieto-insular brain function (Aim 2) or circulating miRNA-485 (Aim 3) may be candidate predictive biomarkers of response to brivaracetam therapy. Collectively, the results of this pilot clinical trial will be used to design larger clinical trials to confirm these hypotheses.

We performed extensive proteomic analyses of electrically hyperactive and normal substantia gelatinosa surgical samples using the SOMAscan platform [Shi et al., 2019]. These spinal cord samples were obtained from SCI patients with excruciating below-level neuropathic pain refractory to all pharmacological management, including Lyrica, Neurontin, and Oxycontin. Proteomic analyses of over 4000 proteins yielded 12 proteins substantially overexpressed in the electrically hyperactive tissue relative to the normal tissue, 5 of these 12 proteins markedly so. One of the 5 proteins found to be markedly overexpressed is the synaptic vesicle protein 2A (SV2A). This protein has been implicated in models of both partial and generalized epilepsy, and the drug brivaracetam (Briviact), which targets and binds SV2A, is used as an FDA approved drug to treat partial-onset seizures. Brivaracetam's effectiveness at treating epileptiform neural activity is attributed to its selective SV2A binding and the binding affinity is 30 times greater than the SV2A agonists levetiracetam (Keppra) [Nicolas et al., 2016].

**Clinical Success with Off-label treatment of SCI Neuropathic Pain with Brivaracetam.** Because epileptiform-like neuronal hyperactivity and elevated SV2A expression is identified in the hyperactive substantia gelatinosa of our SCI patients with below-level neuropathic pain, we elected to treat 2 such patients with brivaracetam for compassionate reasons who had severe pain refractory to all medications, including opioids (e.g. Oxycontin), neuroleptics (e.g. Lyrica, Neurontin), and antidepressant medications (e.g. Cymbalta). These 2 patients were not candidates for our specialized pain surgery because of the risk surgery posed to neurologic function, although they did meet typical selection criteria. Both patients experienced sustained reduction in pain intensity. Patient 1 experienced a 40% (2 point) reduction in average pain intensity and Patient 2 experienced a 66% (6 point) reduction in average pain intensity (figure). This clinical

success provides the scientific rationale for the dosing and treatment duration to be tested in this pilot clinical trial.

**Resting State Brain Functional Connectivity and Neuropathic Pain.** In our ongoing SCI studies, we observe that participants display a wide range of pain levels. As hypothesis-generating preliminary data for this pilot study, we evaluated how variations in neuropathic pain levels impact resting state functional connectivity after SCI. We studied 29 participants with chronic SCI (level C6 or lower) and 11 healthy control participants using 3T MR imaging. A high resolution structural (MPRAGE) dataset and two sets of 6-minute resting state EPI datasets (TR 3 sec) were collected in each participant. Prior to the neuroimaging session, participants rated their current pain levels on a 0 to 10 VAS scale. MRI data was analyzed using the SPM12 based Conn toolbox [Whitfield-Gabrieli and Nieto-Castanon, 2012] (Version 17f, Matlab R2018b). Preprocessing steps included realignment and unwarping, slice-timing correction, ART based identification of outlier scans for scrubbing, segmentation and normalization to MNI space, and 8 mm smoothing. Denoising steps included scrubbing, aCompCor, ICA-based denoising, Global Regression, and 0.008 to 0.09 Hz band-pass filtering. Two main comparisons were evaluated: SCI participants versus uninjured controls, and the effect of concurrent pain ratings on rsfMRI measures. First, we evaluated region-of-interest (ROI) based functional connectivity in a set of anatomically defined regions known to be impacted in SCI and neuropathic pain: the periaqueductal gray, the bilateral thalamus, the amygdala, the hippocampus, the insula, anterior cingulate, the precentral and the post-central gyrus. Second, we evaluated, on a voxel-by-voxel basis, amplitude of low frequency fluctuations (ALFF) and intrinsic resting state functional connectivity. ALFF measures the total power of the BOLD signal within the low-frequency range between 0.01 and 0.1 Hz and is a measure of intensity of low frequency oscillations. Intrinsic resting state connectivity is a measure of how connected a voxel is to other voxels but does not provide information on the regions with which this voxel is connected.

SCI participants reported an average VAS pain of 3.0 (±2.5), ranging from 0 to 8, while uninjured control participants reported an average of 0.26 (±0.64), ranging from 0 to 2. The difference in pain ratings was significant (p=0.00053).

When considering differences between SCI and uninjured controls, we found increased connectivity in the following networks: right amygdala to the left posterior temporal fusiform cortex (pFDR =0.032), left hippocampus to the right frontal pole (pFDR =0.036) the right occipital fusiform gyrus (pFDR =0.025), the right temporal occipital fusiform gyrus (pFDR =0.036), and the

left cerebellum 6 (pFDR =0.036). We also found significantly increased regional brain activity (ALFF) in the paracingulate gyrus (pFDR=0.004).

When considering differences based on the presence of neuropathic pain, we found decreased connectivity in the following networks: right thalamus to the left frontal operculum, (pFDR=0.0002) and left amygdala to the vermis of the cerebellum (pFDR=0.0001). We found increased connectivity in the left amygdala to cerebellum 3 (pFDR =0.0001).

We considering pain rating as a continuous variable, we found a significant positive linear correlation between pain rating and intrinsic connectivity of the post-central gyrus in the somatosensory area of the torso and lower body (pFDR =0.003). We also found a significant positive linear correlation between pain rating and brain activity (ALFF) in the periaqueductal gray area (pFDR=0.0009).

These preliminary findings suggest that SCI disrupts multiple brain networks, along with significant alteration of resting state function of the paracingulate gyrus. Pain may modulate some of these properties, and notably disrupts local brain activity of the periaqueductal gray. The frequency band of ALFF alterations are similar to those of calcium channels and astrocytes, consistent with findings in post-traumatic neuralgia [Alshelh et al., 2016]. Further, the primary somatosensory region representing the lower torso displayed an increase in intrinsic connectivity in parallel with increased pain ratings. This may be consistent with phantom limb like pain, or an increased processing of denervated lower body sensations. Collectively, this work demonstrates feasibility and our expertise with the proposed imaging methodology. ALFF has high test-retest reliability and is thus suitable for longitudinal evaluations [Zuo et al., 2010]. Based on these findings, we hypothesize that brivaracetam treatment will normalize pain-related changes identified above, with ALFF of the periaqueductal gray being the primary outcome. Therefore, these findings provide the scientific rationale for the fMRI studies proposed in Aim 2.

*2.3* Existing Literature:

**SCI Neuropathic Pain.** Neuropathic pain in SCI is associated with decreased pain inhibitory capacity [Albu et al., 2015], and may cause extensive atrophy and reorganization of the CNS [Cragg et al., 2015]. Common pain descriptors used by patients with SCI neuropathic pain include sharp, burning, electric, stabbing, pins-and-needles sensations experienced in regions of anesthesia or hypesthesia. These pains are believed to be of central origin and are often referred to as central neuropathic pains. Pain experienced at the level of injury is referred to as at-level pain and that experienced more than 3

dermatomes caudal to the level of injury as below-level pain. At-level and below-level neuropathic pains are believed to have different mechanisms of central mediation to brain pain centers. At-level pains are believed to originate substantially from electrically hyperactive neuronal activity in the substantia gelatinosa (SG) corresponding to classical somatic dermatomal innervation of the regions of pain experienced. These regions of neuronal hyperactivity are believed to be mediated through classical pain pathways, e.g. spinothalamic tracts, to brain pain centers. Below-level pains are believed to originate substantially from electrically hyperactive neurons in the substantia gelatinosa at the cord level of intermediolateral cell column end organ innervation of perceived pain regions, resulting in a novel somatotopic map of SG below-level pain generators. It is believed that these regions of neuronal hyperactivity are mediated wholly or in part through sympathetic nervous system pathways to brain pain centers.

Dorsal root entry zone (DREZ) lesioning is a surgical method performed only at our center involving operative neurophysiological targeting and ablation of regions of hyperactive substantia gelatinosa that has met with excellent success at relieving severe below-level pains refractory to all forms of pharmacological management this surgical method, 85% of patients with severe below-level neuropathic pain refractory to all pharmacological management achieve essentially 100% pain relief. It is because of this excellent surgical outcome that an IRB study was approved, allowing biopsy of regions of electrically hyperactive substantia gelatinosa and subsequent proteomic analysis, in patients with severe SCI below-level neuropathic pain. Because regions of substantia gelatinosa with normal electrical activity are typically found intermixed with regions of hyperactivity, (these normal regions are typically destroyed in the process of ablation of regions of hyperactivity), biopsies of these normal regions are able to be obtained for proteomic comparison.

**SCI-related Changes in Resting State Brain Connectivity.** Spinal cord injury (SCI) leads to rapid atrophy of the cord above the lesion and to alterations in brain structure and function. This is initiated by direct effects of spinal nerve damage and immediate secondary inflammatory responses. The central nervous system (CNS) changes continue via adaptive and maladaptive plasticity, persistent reactive microglia, and physiological consequences of living with paralysis. Recent studies indicate that the resting state sensorimotor network is disrupted after SCI [Hou et al., 2014] and that the development of chronic pain has a physiologic basis in altered brain structure and function. Specifically, individuals with SCI display decreased inter-hemispheric functional connectivity between the bilateral primary

sensorimotor cortex, as well as increased intra-hemispheric functional connectivity within the motor network. Further, Nictora et al [Nicotra et al., 2006] found that people with SCI displayed enhanced responses within dorsal anterior cingulate cortex and periaqueductal gray during the processing of threat. After SCI, there are also rapid and extensive reductions in gray matter volume in the primary somatosensory cortex lower body, leg, and foot areas [Solstrand Dahlberg et al., 2018]. The degree of atrophy likely depends on the level and completeness of the lesion, the time since injury, and on the presence of pain, but there is disagreement as to how these factors may interact. In a longitudinal study over the first 12 months post SCI, Freund et al. found gray matter volume reductions in the leg area of the primary motor cortex, but not the somatosensory cortex [Freund et al., 2013], and progressive reductions over time were observed in the thalamus, anterior cingulate, secondary somatosensory cortex (part of the parietal operculum), insula and pons [Ziegler et al., 2018]. Such changes in volume related quantitatively to sensory deficits, but there were no correlations between neuropathic pain and volumetric declines during the first year of injury. On the other hand, Jutzeler et al. reported reductions in anterior cingulate cortex (ACC), insula, secondary somatosensory cortex, and thalamus volume in SCI patients with and without neuropathic pain compared to controls. Neuropathic pain was associated with increases in ACC and primary motor cortex gray matter, as well as reductions in primary somatosensory cortex and thalamic gray matter [Jutzeler et al., 2016]. Although inconclusive, the above studies indicate that structural reductions rapidly occur in both cortical (sensorimotor cortex, ACC, insula) and subcortical (hippocampus, thalamus, pons) areas following SCI that seem to be influenced by time since injury and the clinical state (i.e. presence of neuropathic pain).

**microRNA and Neuropathic Pain.** microRNAs (miRNA) have emerged as important biomarkers and molecular mediators in numerous physiological and pathological settings. miRNAs are short, non-coding single-stranded RNA molecules with the ability to exert post-transcriptional modulation of large sections of the genome by binding to regulatory gene elements and inhibiting the translation of many genes [Bartel, 2009; Lagos-Quintana et al., 2001]. They bind to untranslated regions of genes with sometimes imperfect complementarity, which allows for one specific miRNA molecule to inhibit the translation of multiple genes. They are found in every human tissue and biofluid, are resistant to RNAse degradation and have the ability to cross the blood brain barrier making them an excellent choice as a biomarker for neuro-trauma related conditions, neuro-recovery, and response to various therapeutic interventions [Liu and Paroo, 2010].

Significant alterations in microRNAs expression (together with the resultant changes in protein expression) have been reported in both the affected tissues and in the blood from patients suffering from several pain conditions such as complex regional pain syndrome, cystitis-induced chronic pain and irritable bowel disorder. Spinal cord injury-induced neuropathic pain represents a significant clinical challenge that affects 20-77% of injured persons. Specific changes in protein expression in peripheral nociceptive and central neurons are thought to contribute to the development of hyper-excitability which is at the basis of the genesis and persistence of chronic neuropathic pain [Gold and Gebhart, 2010]. Because SCI-induced neuropathic pain is mediated by, among other factors, neuronal protein expression, the process can potentially be regulated by miRNAs. Many studies have been conducted in rodent models of neuropathy investigating changes in miRNA expression both centrally and peripherally. Most of them have demonstrated dysregulation in numerous miRNAs [Bali et al., 2014; Genda et al., 2013; Wu et al., 2011]. In one particular study [Imai et al., 2011], the authors found that a lesion in the periphery (sciatic nerve) caused downregulation of specific miRNA centrally (in post-synaptic neurons of nucleus accumbens). Furthermore, the authors proposed that these changes may be involved in the development of co-morbid conditions like anxiety and sleep disorders, typically associated with persistent pain stimuli. Despite some discrepancies in the literature of this emerging research field, there is a general consensus in that miRNA alterations that occur both in the CNS and the PNS mediate or are associated with neuropathic pain.

The study of miRNA in neuropathic pain is a relatively new field of research. However, the significance of miRNA alterations in a variety of rodent pain models and in clinical conditions characterized by pain has been clearly established (there are more than 30 publications in 2019 alone). The majority of these studies have been conducted in animal models. However, a few studies also describe changes in miRNAs-signatures in complex regional pain syndrome [Orlova et al., 2011] and irritable bowel syndrome-patients [Zhou et al., 2010]. There is evidence that a specific miRNA might play a role in the pathogenesis of neuropathic pain in SCI. miR-485 regulates presynaptic expression of SV2A and regulates dendritic spine density and synapse morphology and function [Cohen et al., 2011]. Synaptic plasticity is a homeostatic response essential to adapt neural circuit connectivity and excitation in response to neurotrauma. miRNA-485 expression is regulated in a number of neurological diseases and after brain trauma. For instance, miRNA-485 is down-regulated in Huntington disease [Packer et al., 2008], Alzheimer's disease [Cogswell et al., 2008], and traumatic brain injury [Redell et al., 2009]. These disease studies, together with our findings that SV2A

expression is increased in individuals with neuropathic pain, suggest that decreased levels of miR-485 with corresponding increased levels of SV2A and neural network activity in nociceptive neurons may contribute to the pathophysiology of SCI-induced neuropathic pain.

Because miR-485 regulates SV2A expression, the target of brivaracetam, we hypothesize that circulating miR-485 may be a valuable predictive biomarker of response to therapy. That is, we hypothesize that individuals with lower circulating miR485 levels may be less likely to respond to brivaracetam treatment for neuropathic pain than those with higher circulating miR485.

miRNAs are promising molecules with potential use as prognostic and diagnostic biomarkers of neuropathic pain and also as predictive biomarkers to monitor the effect of treatments for neuropathic pain in humans. However, the lack of properly conducted clinical studies prevents the bench-to-bedside translation of this knowledge to the clinical setting. This project aims to address these gaps by studying the role of miRNA in SCI neuropathic in humans as well as miRNA signatures as predictive biomarkers of response to brivaracetam therapy in SCI. This evidence provides the scientific rationale for the studies proposed in Aim 3.

## 3.0 Study Endpoints/Events/Outcomes

Primary Endpoint/Event/Outcome:

Our primary endpoint will be reduction in pain intensity assessed by the International Spinal Cord Injury Pain Data Set.

Secondary Endpoint(s)/Event(s)/Outcome(s):
Secondary outcomes include brain resting state and task based activity and functional connectivity and various psychosocial factors related to participants' experiences with SCI, such as change in mood, satisfaction with life, community integration, sleep, self-efficacy, pain catastrophizing, perceived disability, and spasm frequency.

## 4.0 Study Intervention(s)/Investigational Agent(s)

Description:
Intervention: brivaracetam or placebo administration. Dr. Morse (Co-I/study physician) currently holds an Investigational New Drug (IND) application for brivaracetam to treat severe neuropathic pain in individuals with SCI (IND # 150388). With regulatory support provided by UMN CTSI, we will submit this protocol to the FDA for review under the existing IND upon notification of funding. RxArtisans Pharmacy (Wayzata, MN) will FedEx the drug to the participant directly (study staff will send an email notification to the participant that the drug has been sent by overnight

mail) or to the designated contact at the enrolling site for distribution. To minimize wasting of drug, RxArtisans will dispense and ship prescriptions concurrent with the ramp-up schedule (weekly, biweekly, or as requested by study doctor). Participants will be asked to verify by phone or email receipt of study drug and initiation of the treatment course.

Drug dosage will be individually titrated for each participant with a goal of 100mg BID according to the following dose escalation protocol that we use clinically: 50mg BID for 1 week followed by 100mg BID for 28 days as tolerated. Participants will be allowed to reduce the dose of brivaracetam if they experience unacceptable side effects defined as increased somnolence according to routine clinical practice with other drugs in this class used for pain. Participants will be given an additional week to ramp up to 100mg BID, as needed. The 28-day treatment period might also be extended in the case of illness or other unanticipated event that impacts the ability to take the medication consistently. This will be determined on a case-by-case basis by the study team. The treatment course will be recorded and considered in analysis. A dose of 50mg BID or higher must be maintained to complete the trial. The study drug will be paid for by the study.

Drug discontinuation at study completion will be done according to the following protocol we use clinically that will be initiated for 2 weeks following end of study testing (Visit 3): reduction to 50mg BID for 1 week followed by 50mg daily for 1 week. For those at the highest study tolerated dose of 50mg BID, the dose will be reduced to 50mg daily for 1 week and then stopped. At the end of the two-week ramp down, participants will mail any remaining pills and the empty pill bottle along with the medication diary using self-addressed and prepaid packaging. University of Minnesota Investigational Drug Services (IDS) will register the study, while Rx Artisans will be dispensing the drug.

If a participant is admitted to the hospital for any reason during the course of the study, the participant or physician will notify the study coordinator or study PI using the phone number contained on the consent form or printed on the medication bottle. The PI/study coordinator will immediately notify the blinded study physician (Dr. Morse) who will contact the unblinded medical monitor (Dr. Stillman). The two will decide whether unblinding is warranted. If warranted, the medical monitor will access the unblinding key that is stored in a password-protected file that only he and the pharmacy can access. The medical monitor will follow up with the treating physician and provide

the drug information (i.e., placebo or study drug) within 30 minutes of notification. The process for emergent unblinding will be available 24 hours a day, 7 days a week.

At the beginning of the study, all participants are directed that if in this situation, they are to bring study medication to the hospital and inform the physician overseeing the hospital stay that they are taking a research-related study drug. Further, the medical professional should assume that they are on the study drug. He/she may reach out for more information about the study drug.

Drug/Device Handling:
Brivaracetam or placebo will be compounded and dispensed by RxArtisans Inc. The active drug will be placed without modification into the appropriate gelatin capsule. Each strength of active and placebo will have an identical capsule color and inactive ingredients (microcrystalline cellulose and silica gel). Study investigators will send a prescription to the pharmacy, and the pharmacy will dispense the appropriate study medicine. The study medicine will then be provided to research volunteers at UMN or via FedEx/courier delivery in the United States. Study staff will confirm with each participant by phone (or participant-preferred communication including email, text, etc.) that the drug was received.

Biosafety: N/A
Stem Cells: N/A
Fetal Tissue: N/A

## 5.0 Procedures Involved

Study Design:
This is a randomized, double-blind, placebo-controlled clinical trial in 40 adults at least 18 years of age with SCI. Participants who meet the eligibility criteria (described in Section 8.1) will be randomly assigned with a 1:1 ratio to active drug (escalating brivaracetam dose to 100 mg twice daily for four weeks) or placebo using a randomization schedule developed by our biostatistician. This is a simple computer generated 1:1 scheme that randomly assigns participants to arm C or arm D. Study participants, research coordinators, and study personnel involved in outcomes assessments and analyses will all be masked to allocation. The drug will be provided by RxArtisans pharmacy in Wayzata, MN. The active and placebo capsules will have identical appearance and consistency. Treatment assignment will be known only to the investigational drug pharmacy (RxArtisans). We will register this trial at www.clinicaltrials.gov.

Study Procedures:

Overview of study procedures/study interventions. This study involves research activities that occur in-person, over the phone, and via online REDCap surveys. Participants will also have the option to participate entirely remotely. In this circumstance, there will be no MRI scan nor blood draw for banking; instead, all required safety labs will be completed with the participant's primary care physician and insurance will be charged and the participant will be responsible for any associated copays or costs. All research activities are summarized in Table 1 below and described in detail in the subsequent text.

*Screening:* A phone screen will be administered to confirm basic eligibility criteria listed in Section 8.1 such as age, pain level, medication use, and other medical conditions. Study staff will also screen for MRI contraindications at that time with the Center for Magnetic Resonance Research (CMRR) pre-screening questionnaire (i.e., implanted medical devices or retained metal fragments). Eligible individuals will be required to receive medical clearance from their primary care provider within one month of (prior to) Visit 1, including physical exam, health history, and lab work to confirm normal renal function, absence of liver cirrhosis, and absence of pregnancy. While we will target obtaining lab work within 1 month of baseline, labs up to 6-weeks prior to baseline will be accepted to reduce participant burden. Their insurance will be charged, and they will be responsible for any associated copays or costs.

For participants who recently had comprehensive metabolic panel done, medical record review of lab results can replace new screening labs if the blood labs were completed within one month of (prior to) the scheduled baseline appointment. If the participant is seeing a provider in-system, the study coordinator will pull labs from the medical record. If the participant is not seeing a provider in-system, the study coordinator will instruct the participant's physician to fax the lab report to the study coordinator. The instructions for faxing will be on the screening eligibility sheet the participant brings to their doctor's appointment and available to be emailed for the participant upon request.

*Visit 1:* This visit includes informed consent, randomization, a focused physical exam, and a mental health and health history screen. CDE-recommended questionnaires relating to pain, mood, active suicidality, satisfaction with life, kinesiophobia, sleep quality, and community integration will also be administered.

*Visit 2:* This visit may be combined with Visit 1, if the participant prefers. Visit 2 includes an optional blood draw for batch analysis and an optional MRI scan; the optional MRI and optional blood draw are paid for by the study. Visits 1 and 2 can take place either at the study site or virtually, depending on participant preference. Those who choose to participate in the study virtually will not take part in the MRI or blood draw. For participants with contraindications to MRI, the MRI will not be completed.

Once randomized, the 7-week supply of study drug will be dispensed and mailed directly to participants to begin 7 weeks of active treatment or placebo, as described in Section 4.0. All participants will receive a medication diary to track study drug compliance and to record medication use.

*Weekly phone check-in*: Masked data collectors will perform weekly check-in calls to assess for medication-related adverse events (AEs). The data collector will also administer the Patient Health Questionnaire 9-item (PHQ-9) to assess for changes in mood and suicidality. A suicide protocol will be initiated if a participant endorses suicidality (see below). Participants will also report on their level of pain (rate highest, lowest, and average pain (0-10) that day). Reported AEs identified in these calls will be documented and immediately shared with the PI for review.

*Suicide Protocol:* Endorsement of active suicidality on PHQ-9 will trigger the suicide protocol. Study staff will call 911 in the event of a psychological emergency noted during a phone call (credible report of intent to harm oneself). Study staff will first ask to speak to another adult in the household. If none is present or comes to call, study staff will call 911 and remain on the line until first responders arrive. In the event of a non-emergent psychological situation (psychological distress in the absence of intent for self-harm), study staff will refer the participant to their PCP or the National Suicide Hotline (1-800-SUICIDE). In either case, study staff will notify the PI immediately.

*Visit 3:* End of intervention assessments will be repeated 5 weeks after Visit 2. This includes a focused physical exam, a mental health and health history screen, optional blood draw, optional MRI, and questionnaires relating to pain, mood, active suicidality, satisfaction with life, kinesiophobia, sleep quality, and community integration. Additionally, limited safety labs will be repeated (from pre-Visit 1) to confirm normal renal function, absence of liver cirrhosis, and absence of pregnancy in individuals of childbearing potential. The fasting blood draw and analysis

will occur either at the enrolling site or with the participant's primary care provider, based on participant preference. Blood will be analyzed for blood urea nitrogen (BUN), creatinine, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, albumin, GFR, calcium, corrected calcium, and human chorionic gonadotropin (hCG); urine hCG test will also be accepted. International normalized ratio (INR) will be collected at the discretion of the participant's primary care provider if the participant is on anticoagulation or has abnormal liver function tests. People who are menopausal and have not had a menstrual period for at least 12 months, or people who have had a hysterectomy will not be required to take pregnancy tests. Results of the pregnancy test will be sent only to study staff. At the end of Visit 3, study staff will provide instruction for the first week of the two-week dose reduction period. Data collectors will continue weekly check-ins throughout the ramp down period and up until Visit 4. Data collectors will also remind the participant to return the remaining pills and pill bottle along with the medication diary using the pre-paid envelope provided by study staff.

*Visit 4:* Visit 4 occurs 1 month following the end of study drug. Data collectors will assess for AEs, changes in mood and suicidality via the PHQ-9, medications, and pain levels; surveys related to mood, satisfaction with life, community integration, fear of movement related to pain, and sleep will also be administered at this time.

Our primary endpoint is reduction in pain intensity assessed by the International Spinal Cord Injury Pain Data Set. Secondary outcomes include reduction in opioid use, change in mood, satisfaction with life, community integration, brain resting-state functional connectivity, and task-based brain activation and connectivity, sleep, neuropathic pain, self-efficacy, pain catastrophizing, perceived disability, spasm frequency, and intervention expectations. The specific study measures are listed below:

*International Spinal Cord Injury Pain Data Set.* This tool assesses average pain intensity in the last week using a 0-10 numerical rating scale. The 0-10 numerical rating scale has been recommended by the IMMPACT consensus group for use in pain clinical trials [Dworkin et al., 2005] and by the 2006 NIDRR SCI Pain outcome measures consensus group. [Bryce et al., 2007] This scale is recommended to standardize pain outcomes across studies. The International Spinal Cord Injury Pain Data Set also assesses dimensions of pain (i.e., intensity of pain, time of day, location, occurrence, etc.), and pain interference with mood, activity, and sleep.

*Modified Brief Pain Inventory (BPI)*. The BPI is a short self-assessment questionnaire that provides information on various dimensions of pain including how pain developed, the types of pain a patient experiences, and time of day pain is experienced, as well as current ways of alleviating pain [Cleeland and Ryan, 1994]. The BPI also consists of the numeric pain rating scale, a simple 10-point scale (0 = ''no pain'', 10 = ''pain as bad as you can imagine'') measuring a patient's worst pain and least pain, on average in the last 24h and at present time. The Brief Pain Inventory provides information on the intensity of pain (the sensory dimension) as well as the degree to which pain interferes with function (the reactive dimension). According to several previous studies on pain in spinal cord injury, the BPI is an effective measure [Bryce et al., 2007].

*DN4 Assessment Tool.* This is a 4-item assessment that characterizes neuropathic pain.

*Assessment of Mood with the Patient Health Questionnaire (PHQ-9).* This is a 9-item scale that assesses patient quality of life through mental state. It identifies active suicidality [Kroenke et al., 2001]. It assists physicians in both diagnosing depression and determining a treatment route. It incorporates DSM-IV depression classifications and determines severity of depression [Bombardier et al., 2004; Graves and Bombardier, 2008; Kalpakjian et al., 2009; Krause et al., 2010].

*Satisfaction with Life Scale (SWLS).* This is a 5-item scale that assesses patient happiness with current quality of life [Diener et al., 1985]. It consists of a 1-7 Likert scale.

*Craig Handicap Assessment and Reporting Technique – Short Form (CHART-SF*). This assessment is commonly used to provide an objective measure as to the degree by which a person with SCI remains with impairment or disability [Whiteneck et al., 1992]. It measures several domains including: the type and level of daily assistance needed on both a physical and cognitive level (i.e., personal care, hygiene, decision making, communicating with others); level of physical activity (ranging from travel to daily mobility); transportation needs how time is spent (i.e., employment, housekeeping, cooking, leisure activities); social interactions (including relatives, co-workers, and friends); and available financial resources.

*Posttraumatic Stress Symptoms (PTSS).* The PTSD Checklist for DSM-5 (PCL-5) is a 20-item self-report measure assessing symptoms of PTSD.

Participants rate how bothered they have been by each of the 20 items in the past month on a 5-point scale ranging from 0 (not at all) to 4 (extremely). Scores range from 0-80, with higher scores indicating greater severity of PTSD symptoms. The PCL-5 is psychometrically sound in civilians and Veterans.

*Childhood Trauma.* The Adverse Childhood Experiences Questionnaire (ACE-Q) is a 10-item measure to quantify instances of adverse or traumatic experiences that a person has had before the age of 18. The ACE-Q will be asked at baseline and screens for exposure to childhood psychological, physical, and sexual abuse as well as household dysfunction including domestic violence, substance use, and incarceration.

*Pittsburgh Sleep Quality Index.* This is a 9-item scale that assesses sleep quality.

*Tampa Scale for Kinesiophobia.* This is a 17-item scale that assesses fear of movement.

*Moorong Self-Efficacy Scale (MSES).* This is a 16-item scale that assesses self-efficacy in performing functional activities of daily living individuals with SCI.

*Pain Catastrophizing Scale (PCS).* This 13-item self-report measure is designed to assess catastrophic thinking related to pain among adults with or without chronic pain.

*Perceived Disability Index (PDI).* This is a brief, self-report instrument developed to assess self-perception of disability.

*Penn Spasm Frequency Scale (PSFS).* This is a self-report measure that assess a patient's perception of spasticity frequency and severity following a spinal cord injury.

*Bladder and bowel function.* Nine self-report items will assess current bladder and bowel functioning.

*Intervention Expectations.* This self-report will assess what participants expect their outcomes to be during and after their participation in the study.

*Study Expectancies.* Participants respond to 24 items about how they think they will function 7 weeks from now in areas such as pain, sleep, participation, work, social activities, and sexual functioning.

*Concurrent Pain Medication Use.* Although pain medications can confound the analgesic effects of brivaracetam, we consider it to be unethical to require participants to discontinue pharmacologic treatment for pain over the course of the study as a criterion for enrollment. In addition, to increase generalizability, it is important to recruit participants using pain medications. Therefore, we will record pain medication use over the course of the trial and consider this in the analysis.

*Pain Intensity and Medication Use Diary.* We will monitor daily pain reports and patient medication throughout the course of the study using a Pain Intensity and Medication Use Diary. Participants will be asked to record daily pain ratings (highest pain 0-10, lowest pain 0-10, and average pain 0-10) and any pain medication use. This diary will be started 1 week prior to drug treatment and maintained until completion of the study.

*Assessment of Brain Function with MRI.* All scans will be performed on the same scanner for this study. We will use the Siemens 3-T Prisma multi-band scanner. Prior to each scan, participants will be asked five questions regarding their pain now and over the last week as well as alcohol, caffeine, and tobacco use over the past 12 hours.

1. Structural MRI acquisition: We will acquire a T1-weighted Magnetization-Prepared Rapid Acquisition with Gradient Echo (MPRAGE) image [Repetition Time (TR)=2.5s, Echo Time (TE)=4.5ms, 0.8mm$^3$ voxels], and a $T_2$ weighted Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE) image [TR=3.2s, TE=565ms, 0.8mm$^3$ voxels]. We use special sequences for the scans to reduce the impact of head motion.

2. Resting-state and task fMRI acquisition: The resting-state and task fMRI scans will be obtained with a T2*-weighted multiband echo planar acquisition tipped 30 degrees relative to the Anterior Commissure - Posterior Commissure (AC-PC) plane as determined by the auto-align software. This acquisition protocol is designed to measure whole-head BOLD-contrast with optimal temporal and spatial resolution, and to reduce signal dropout [TR=0.8s; TE=37ms; Flip Angle=55$^o$; 72 slices;multiband factor 8; 2mm isotropic resolution]. We will use the Framewise Integrated Real-time MRIMonitoring (FIRMM)

software to track head motion for each fMRI scan in real time. If visual inspection or FIRMM shows that image quality is substandard, the scan will be repeated immediately. After the MRI acquisition, a structured Quality Assurance (QA) process will occur within 72 hours to ensure that the data are of sufficient quality for subsequent analysis. Adhering tothese QA procedures should result in over 95% usable data.

i. Task 1: Mental body scan. Participants will be asked to focus with gentle, non-judgmental awareness on the sensations of the leg (that they experience having the most pain). In other words, they perform a gentle focused mental body scan and register any feelings of sensation in that limb. We alternate this task with rest periods. We chose Task 1 based on our previous study in adults with chronic low back pain showing OP1/OP4 and posterior parietal cortex activation after body awareness training during a similar task. Other brain imaging research showed that doing a mindful mental body scan significantly increases insula connectivity.
ii. Task 2: Kinesthetic imagery of moving the limb. Participants will be asked to imagine the feeling of gently moving the painful leg (i.e., gentle non-judgmental awareness of any sensations during an imagined movement), alternated with rest. We chose this task based on tasks with mindfulness meditation showing insula and OP1/OP4 activation.
iii. Task 3: Whole-body movement task. Participants will perform a kinesthetic imagery of a whole-body movement, in which the hands are moving away and closer to the body symmetrically with guided breathing after viewing a video demonstration of the movement. We chose task 3 based on studies that demonstrate substantial spatial overlap of areas activated during motor imagery vs. motor execution. Our prior studies showed OP1/OP4 and posterior parietal cortex activation during this task in adults with chronic low back pain. We showed stronger insula connectivity after CMR in adults with SCI/D.
iv. Task 4: Sensory stimulation task of the pads of the big toes and thumbs with a towel. Participants will not be made aware of when stroking occurs and will be asked after the scan if they sensed any hand or foot stimulation and, if so, where exactly they felt the stimulation.
v. Task 5: Finger tapping. The participant is instructed verbally to tap their right fingers

vi. Task 6: Toe tapping. The participant is instructed verbally to tap their right foot. The task is alternated with rest.

**Table 1. Study Procedures**

| Study Task | Screening | Visit 1[b] | Visit 2[b] | 7-week intervention | Visit 3[c] (end of study testing) | Visit 4[c] |
|---|---|---|---|---|---|---|
| Screening Phone Survey | X | | | | | |
| Consent/randomization | | X | | | | |
| MRI Brain Scan (optional) | | | X | | X | |
| Blood draw for biomarkers (optional) | | | X | | X | |
| Physical health exam, health history screening | | X | | | X | |
| Surveys | | X | | | X | X[c] |
| Dispense study drug | | | X | | | |
| 7-week drug intervention | | | | X | | |
| Limited safety labs (blood draw, required) | X[a] | | | | X | |
| Pregnancy test (for women of child-bearing potential) | | | | | X | |
| Drug dose reduction protocol | | | | | X[c] | |
| Participant return remaining pills, bottle, and medication diary via mail | | | | | X[c] | |
| Adverse Events, PHQ-9, pain rating (highest, lowest, average) | | | | Assessed weekly[c] | | |

PHQ-9: Patient Health Questionnaire 9-item
[a]Medical clearance must be clinically obtained from participants' primary care provider or other healthcare provider within 1 month prior to visit 1
[b]Visits 1 and 2 may be combined for participant convenience
[c]Performed at the time of early withdrawal for those not completing the study

*Study drop criteria*: Participants will be removed from the study for safety reasons including drug intolerance, drug allergy, drug contraindications, development of depression, aggressive behavior, anxiety, or suicidality, or evidence of brivaracetam adverse events according to the manufacturer's prescribing guide (package insert). Poor drug compliance will be recorded for consideration during the analysis but will not be cause for removal from this study. In the case of drug intolerance, participants will reduce the drug dose under medical supervision of the PI until the drug can be safely discontinued.

Study Duration:
This is a 5-year study. Eligible participants will be enrolled throughout the duration of the study. It is anticipated that study enrollment goal will be met six months prior to study ending in year 5. Individual participant's participation will approximately be 11 weeks from time of enrollment into the study. We anticipate the completion of all study procedures, including data analysis and results to report, will take approximately a year once the study has completed all data collection from study participants.

Use of radiation*: N/A*

Use of Center for Magnetic Resonance Research*:*
All participants who consent to MRI testing will get a 3T structural and functional MRI scan at Visit 2 and after completion of the 7-week treatment course (Visit 3). They will use the changing room to change into scrubs according to the CMRR protocol.

## 6.0 Data and Specimen Banking

*6.1* Storage and Access:

All data used for this project will be obtained after receiving informed consent from all participants. The research material collected in this project are in the form of: (1) magnetic resonance imaging (MRI) records, (2) standardized patient-rated questionnaires, clinical assessments, and (3) blood serum.

Clinical data will be stored on Research Electronic Data Capture (REDCap), physical paper files will be kept in a locked file drawer in the study coordinator's office, and on encrypted servers (Box). Participant confidentiality will be safeguarded by the use of password protected databases and locked file cabinets. Research records will be stripped of all identifying information, with keys identifying individual participants available only to the PI or selected designees. Further, access to identifiable private information from study participants will only be accessible to study-related personnel who have met the training requirements for the responsible conduct of research, Good Clinical Practice, HIPAA, and data security, and who have completed all initial and annual study specific training.

Blood samples will be collected at each enrolling site and stored locally in a -80 freezer at UMN. Blood samples will be labeled by ID number, type (plasma or serum), and date of draw. A password-protected tracking sheet will be used to link participants' blood samples with identifiable information

(i.e., date of birth). This sheet will only be accessed by the IRB-approved study staff.

At the baseline and final evaluation, we will draw 38 ml of blood (20 mL plasma, 18 mL serum) after an overnight fast and store it at -80° Celsius until batch processing in the lab of the PI.

*6.2* Data:

All clinical assessments and standardized patient-rated questionnaires will be stored on Research Electronic Data Capture (REDCap) and on encrypted servers.

Imaging of brain activation and connectivity (resting-state and task-based fMRI), will be preprocessed using the HCP preprocessing pipeline. MRI data will be stored in digital form on encrypted servers.

We will bank blood serum and plasma for long-term storage. To minimize the risk of loss of privacy all records will be kept confidential and identified by study code only in the working databases. Blood samples will be stored without identifiers using only the study code.

*6.3* Release/Sharing:

The results will be submitted for publication in scientific journals and presented at conferences. In case the scientific journals request the original database, the de-identified Excel file with scoring and codes will be shared on their protected databases.

## 7.0 Sharing of Results with Participants

*7.1* Sharing Results:

No information will be provided to the participant unless the information indicates that the participant may be at risk for a serious illness known at the time of testing to be treatable. In that case, the study doctor will attempt to notify the participant. The research participant and their clinical care person(s) are responsible for further evaluation/follow-up in response to MRI incidental findings. Participants will be given the option to opt out of receiving any incidental findings.

*7.2* Sharing Genetic Results: N/A

7.2.1 Disclosure of Results: N/A

7.2.2 Returning Results to Participants: N/A

Aggregate or individual results: N/A

Laboratory results: N/A

Plan for return of results to participants: N/A

Types of results to be returned to participants: N/A

7.2.3 Future analysis of genotypes: Future genome sequencing may be conducted but will not be used for clinical diagnosis and will not have any clinical utility.

## 8.0 Study Population

Inclusion Criteria:

- 18 years of age or older
- Injured for ≥ 3 months
- Completed inpatient rehabilitation and living in the community
- Chronic sublesional neuropathic pain defined as persistent pain (VAS grade 3-10) for three months or more
- For people of child-bearing potential: currently practicing an effective form of two types of birth control (defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly).

Exclusion Criteria:

- Progressive myelopathy secondary to posttraumatic cord tethering or syringomyelia
- Active use of drugs known to interact with brivaracetam: rifampin, carbamazepine, sodium oxybate, buprenorphine, propoxyphene, levetiracetam, and phenytoin.
- Brain injury or cognitive impairment limiting the ability to follow directions or provide informed consent
- Pregnancy or lactation
- Epilepsy or active treatment for seizure disorder
- Past or current suicidality
- Active treatment for psychiatric disease
- Drug addiction
- Moderate or heavy alcohol intake (up to four alcoholic drinks for men and three for women in any single day, and a maximum of 14 drinks for men and 7 drinks for women per week)

- Hepatic cirrhosis, Child-Pugh grades A, B, and C
- Impaired renal function (GFR<60ml/minute)
- Contraindications to brivaracetam or pyrrolidine derivatives including allergy
- Active clinically significant disease (e.g., renal, hepatic, neurological, cardiovascular, pulmonary, endocrine, psychiatric, hematologic, urologic, or other acute or chronic illness) that, in the opinion of the investigator, would make the patient an unsuitable candidate for this trial.
- History of malabsorption or other gastrointestinal (GI) disease that may significantly alter the absorption of brivaracetam
- Use of any investigational drug 30 days prior to enrollment in this study
- Dependent on mechanical ventilation.
- Use a gastrostomy tube (G-Tube) for feeding.
- Enrollment in another clinical trial.

People with contraindications to MRI including retained bullet fragments, noncompatible metal implants, and implanted devices such as non-MRI compatible baclofen pumps may still be eligible for the study; they will not participate in the MRI scans.

Screening:

A phone screen will be administered to confirm basic eligibility criteria listed in Section 8.1 such as age, pain level, medication use, and other medical conditions. For those that agree to have an MRI, we will screen participants for contra-indications for MRI compatibility with the CMRR pre-screening questionnaire. If participant meets basic eligibility requirements, we will request that they obtain medical clearance for study participation from their primary care provider or other medical professional, including collecting 3-4 tablespoons of blood for screening blood work (described in detail below) and completing a physical exam and health history. This must be conducted within 1 month (or up to 6-weeks) of Visit 1. The participant's insurance will be charged, and they will be responsible for any associated copays or costs.

The participant's provider will send research staff the results via fax or email, or the participant may carry a hard copy to Visit 1. If a patient is part of the enrolling site's system of care, their medical records will be accessed directly by research staff who have obtained the appropriate approvals (e.g., NERS approval).

*Screening bloodwork for hepatic cirrhosis, renal insufficiency, and pregnancy*. Brivaracetam treatment is not safe for those who are pregnant, have hepatic cirrhosis, or kidney dysfunction. Therefore, to be medically cleared to enter the study, participants must complete a fasting blood draw through their primary care clinic for analysis of blood urea nitrogen (BUN), creatinine, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, albumin, GFR, calcium, corrected calcium, and human chorionic gonadotropin (hCG); urine hCG test will also be accepted. International normalized ratio (INR) will be collected at the discretion of the participant's primary care provider if the participant is on anticoagulation or has abnormal liver function tests. People who are menopausal and have not had a menstrual period for at least 12 months, or people who have had a hysterectomy will not be required to take pregnancy tests. We will use lab work performed clinically during any recent visit (within one month or up to 6-weeks of testing) for screening labs when available. Any participant found to have renal insufficiency (GFR<60ml/minute), hepatic cirrhosis, Child-Pugh grades A, B, and C, or pregnant (positive hCG) will be considered a screen fail and will not progress in the study.

## 9.0 Vulnerable Populations

Vulnerable Populations:

| Population / Group | Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from participation in the study. |
|---|---|
| Children | Excluded from Participation |
| Pregnant women/fetuses/neonates | Excluded from Participation |
| Prisoners | Excluded from Participation |
| Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders | Excluded from Participation |

| | |
|---|---|
| Non-English speakers | Included/Allowed to Participate |
| Those unable to read (illiterate) | Included/Allowed to Participate |
| Employees of the researcher | Excluded from Participation |
| Students of the researcher | Excluded from Participation |
| Undervalued or disenfranchised social group | Included/Allowed to Participate |
| Active members of the military (service members), DoD personnel (including civilian employees) | Included/Allowed to Participate |
| Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc. | Excluded from Participation |
| Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare. | Included/Allowed to Participate |
| Individual or group with a serious health condition for which there are no satisfactory standard treatments. | Targeted Population |
| Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior). | Excluded from Participation |
| Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research. | Excluded from Participation |

Additional Safeguards:

This project aims to research an intervention that may help vulnerable adults with spinal cord injuries reduce severe neuropathic pain, a severe health condition. To provide additional safeguards to protect individuals that may be vulnerable we:

- Will provide assurance of confidentiality, freedom to decline to participate, right to withdraw at any time without penalty.
- Engaged the SCI community in the planning of this research.
- We have assessed the permissibility of the physician-investigator to obtain consent for research.
- We will emphasize the risks and demands of this study participation to potential participants.
- We will provide short forms and a translator to individuals who are unable to read or speak in English.
- Groups included in the research where participant status in the group might be unknown (incidental enrollment), as group status is not solicited by the research team (ex: military status, if study teams don't ask and it doesn't impact the research):

The vulnerable population groups that are allowed to participate will not be identified and information will not be collected as to a patient's vulnerable population status. This research does not add risk to this group.

## 10.0 Local Number of Participants

Local Number of Participants to be Consented:
We expect to screen 200 individuals to enroll 48 participants. We expect 20% attrition, therefore we anticipate a total of 40 participants will complete the study.

We anticipate enrolling a minimum of 12 participants and up to a maximum of 48 participants.

## 11.0 Local Recruitment Methods

Recruitment Process:

The UMN healthcare system treats hundreds of patients with SCI each year. Given the large pool available for recruitment, we anticipate no difficulty in recruiting sufficient numbers of persons with SCI who meet the inclusion/exclusion criteria. Recruitment material will accurately reflect the study and will not be coercive.

*For self-referrals from recruitment materials:*

Participants may self-refer if they become aware of the study through recruitment materials, clinicaltrials.gov (or similar websites), or word of mouth referrals. A study-specific webpage will be published. A link to a REDCap online survey will be shared for individuals to indicate their interest and preferred contact method. Participants will self-enter their contact information prior to consent for contact purposes only.

Potential participants will be identified by Co-Investigators from patients under their care and their colleagues. Potential participants will be asked about their interest in the study at the time of a routine care visit. If interested, the patient will be given the choice to be approached by the investigator in person, over phone, or via e-mail, or have reach out to the investigator themselves. A flyer or recruitment card about the study may be sent to potential participants, asking them to contact study staff if they are interested.

Individuals who respond to the recruitment materials will complete a phone screen with study staff. If following the phone screen, the potential participant is eligible and interested, they will be required to seek medical clearance from their primary care physician, including a screening blood draw, one month prior to study Visit 1.

*Regional Healthcare Institutions:*
Contacts at regional healthcare institutions that have partnered with the University of Minnesota in previous SCI research will be made aware of this research, including the VA. Flyers and/or postcards/recruitment cards will be posted around campus, at the VA, on the UMN website (e.g., Brain Body Mind Lab website) and on social media with information about this study.

*Patient Representative Organizations (PRO):*
Recruitment information about this study will be provided to PRO's that will include sample text and flyers so they may distribute information about this study to their participating community members living with SCI. PRO's commonly use social media, newsletters, and share information at peer support groups to distribute information about the clinical trial. Targeted PRO's will include but will not be limited to Get Up Stand Up to Cure Paralysis, Minnesota Spinal Cord Injury Association, and Morton Cure Paralysis.

*University of Minnesota Spinal Cord Injury Research Recruitment Registry:*
We will utilize the Spinal Cord Injury Research Recruitment Registry managed by the UMN Department of Rehabilitation Medicine to help

facilitate enrollment. We will filter individuals in the registry based on inclusion/exclusion criteria and contact them via email or phone about this research opportunity.

*Online Clinical Trial Registries*:
This clinical trial will be listed on www.clinicaltrials.gov, www.scitrials.org, and other similar websites that assist community members to find and contact information about clinical trials.

*Local Community Presentations:*
The study team may hold presentations (digital or in-person) about this research and other projects and research results which may inform community members about this clinical trial which may result in recruitment.

*Social Media:*
Digital media may be shared on different social media platforms to notify potential participants about the clinical trial and how to contact the study team.

*Fairview Recruitment Mailing and MyChart Messaging*:
We will work with Fairview Research Services to identify individuals with SCI in the system and send recruitment mailings through the mail and/or MyChart messages, pending approval from the Fairview Research Administration. Patients who have opted out of having their records used for research will not be included.

Identification of Potential Participants:
Participants will be identified from the clinical partnerships listed in section 11.1. Study PI and physicians from our clinical partnerships will identify potential participants from their patient pools. These physicians have access to potential study participants' medical records and knowledge of their health history. Study staff will conduct prescreening over the phone or in-person to confirm eligibility at each site.

*Approaching potential participants in clinic:*
Potential participants will be identified by the Co-Investigator (Dr. Leslie Morse) and her team from among patients under her team's care and that of their colleagues who have legitimate access to their medical records. Through BPIC involvement, EPIC will be searched on the hits provided by BPIC. If eligible, a mailing will be sent out.

*Participants self-referred from recruitment materials:*

Potential participants will self-identify in response to flyer announcements via professional associations or support groups/word to mouth or other means.

We will use following approaches to identify participants through self-referrals:

- Postings on StudyFinder, a website managed by the UMN CTSI's Recruitment Center
- Postings on clinicaltrials.gov
- Identification via UMNs Research Match, an electronic volunteer recruitment registry
- Postings, flyers, or recruitment cards at the University of Minnesota and local rehabilitation centers; relevant websites and on professional social media sites (e.g., Facebook, Twitter).

Recruitment Materials:
The following recruitment materials will be used in this study: flyers or recruitment cards.

Payment:
Participants will receive up to $350 for their time, effort, and to assist with transportation. Participants will receive $150 after baseline testing (Visit 2), $150 after end of study testing (Visit 3), and $50 after Visit 4.

## 12.0 Withdrawal of Participants

Withdrawal Circumstances:
At any time after enrollment, a participant may be discontinued. Reasons for discontinuation of a participant from the study will include, but may not be limited to, the following:

- The participant is found to be intolerant to a required study procedure at any time point
- Failure of the participant to adhere to protocol requirements
- Positive hGC for individuals of childbearing potential
- The participant experiences a serious adverse experience at any time point
- The participant develops an inter-current illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- The participant enrolls in another investigational study
- The participant requests to withdraw from the study

Withdrawal Procedures:
The PI and study physician will work closely with any participant wishing to withdraw from the study to ensure that the study drug is tapered appropriately and safely.
Termination Procedures:
Participation may be terminated due to drug intolerance or allergy and based on clinical judgement of the study team. All data collected will be retained and analyzed unless the participant specifically requests to have their data withdrawn from the analysis.

## 13.0 Risks to Participants

Foreseeable Risks:
There is a risk of drug intolerance including allergy, suicidal behavior and ideation, somnolence and fatigue, psychotic symptoms, irritability, depression, loss of coordination/balance, constipation, aggressive behavior, and anxiety. All participants and caregivers will be educated to notify the PI or a health care provider if mood changes or suicidal behavior is observed. There is the risk of lowered seizure threshold for rapid drug withdrawal without tapering. There is some discomfort with venipuncture and there is the possibility of swelling and bruising at the site. There is also a slight chance that individuals become dizzy or faint. There are potential risks of loss of privacy and confidentiality. All participants will be encouraged to contact study staff, or an investigator regarding any side effects or adverse events that occur.

**MRI**

MRI machines use a strong magnet and radiofrequency magnetic fields to take images of your body. The scanning process is similar to an x-ray or CT scan, but MRI does not use ionizing radiation (high-energy radiation that can potentially cause damage to DNA) like x-rays or CT scans. The risks associated with MRI scans are:

- Projectiles: Objects with magnetic properties can be pulled into the magnet and turn into projectiles. To minimize this risk, we ask that participants remove all metallic items (watches, cell phones, hair pins, etc.) prior to entering the scanner and by controlling access to the scanner.
- Claustrophobia: The scanner is a long narrow tube that may cause some people to feel claustrophobic.
- Hearing Damage: The noise generated by the operation of the scanner during a study is loud enough to cause hearing damage

if hearing protection is not worn. Hearing protection is required and is provided by the investigator.

- Nerve Stimulation: Some people experience localized tingling, twitching, or muscle contractions during MRI scans. We ask the participants to notify the investigator if this sensation is uncomfortable.
- Disruption of Devices: Some devices can be damaged by magnetic fields and should not be brought into the scanner room. This includes some implanted devices such as pacemakers, cochlear implants, insulin pumps, nerve stimulators, etc. If participants have any implanted device, they are asked to notify the investigator.
- Heating of Devices: The radiofrequency waves used in MRI can heat conductive materials. "The research team will utilize the CMRR Center's screening tools and adhere to the screening SOP during enrollment of all research participants in this protocol. The CMRR Center's screening tools and SOP are IRB approved under the CMRR Center Grant (HSC# 1406M51205) and information regarding screening procedures is publicly available on the CMRR website (CMRR Policies / Procedures).

**Venipuncture**

There is some discomfort with venipuncture and there is the possibility of swelling, inflammation, and bruising at the site, and, in rare cases, the risk of infection. There is also a slight chance that individuals become dizzy or faint. All blood draws completed at the study site will be performed by a trained technician following standard clinical protocols to minimize risks.

**Risks Associated with Breach of Confidentiality**

There is a risk of breach of confidentiality. Multiple measures will be taken to minimize this risk. All information that could be used to identify a participant will be kept in a secure and locked space accessible only by the trained study coordinator and the principal investigator. All of these documents will be kept in locked file cabinets, in locked offices, at all times. Also kept secure and separate from other files will be the unique ID for each participant. Information collected will be stored on Box Secure Storage or REDCap. The computers used are password-protected and will only be used by trained study staff and for study purposes only. All blood samples are uniquely coded by number and are "de-identified." Blood samples collected to test for biomarkers will be stored behind locked doors in on-site freezers for an indefinite period of time with only coded numbers

as the key to identity. The key to the codes will be available only to selected investigators. Participants wishing to withdraw their samples from the study may do so at any time by notifying the investigators in writing. There is also a small chance that, if participants engage in a videoconference through the Zoom for Healthcare platform, the Zoom session could be hacked.

**Participant monitoring**
Study staff will monitor and respond to reports regarding adverse events collected during sessions and on self-report questionnaires. Adverse events will also be assessed once per week throughout the study over the phone and entered into a REDCap form. Participants will also be instructed to contact the investigators and/or study staff if they experience a serious adverse event. If an event occurs, protocols for adverse event classification and reporting will be followed.

**Participant confidentiality**
Procedures are in place for maintaining the full confidentiality of all information collected. Participant confidentiality will be protected by securing all hard copy study files in locked filing cabinets. Electronic files containing personal identifiers will be stored on Box Secure Storage or REDCap. All study staff receive training on privacy standards for maintaining participant confidentiality. All published reports will be of summary nature and no individual participants will be identified beyond the investigative staff involved in the project. Electronic data management is described above (see 'Data Coordination').

Reproduction Risks:
**Pregnancy**
We are excluding pregnant or lactating people from this study.

Risks to Others: N/A

## 14.0 Potential Benefits to Participants

Potential Benefits:
Because this study will be used to develop clinical trials for testing pharmacological interventions to treat neuropathic pain in SCI, there is a potential future benefit to the spinal cord population.

## 15.0 Statistical Considerations

*15.1* Data Analysis Plan:

For Aim 1, the first step for each outcome variable (e.g., pain,) is an unadjusted comparison across the groups as randomized. Each of the outcome variables uses a pre-defined instrument which has both top and bottom boundaries. These bounds are, however, wide enough so that the first steps will ignore the boundaries. The first analysis in each case is an unadjusted analysis and will be done in two ways: (1) a t-test (assuming unequal variances) and (2) a rank-sum test to take advantage of the Mann-Whitney score, which provides the probability that one group will have scores greater (less) than the other group. This statistic is the same as the c statistic widely used after logistic regression. The next step for each outcome is regression model with the main predictor being an indicator group. Standard covariates (e.g., demographics, and measures relevant to SCI such as severity and time since injury) will be included in the analysis. Robust estimator of the standard errors will be used. Predicted values will be checked to see whether any, and, if so, how many, are outside the boundaries of the measure used for that outcome. As a sensitivity analysis, regression models that recognize the boundaries will be used (e.g., fractional logistic regression or two-limit Tobit models). The main analysis will be Intention-to-Treat.

For Aim 2, we will use the same analytic approach we have refined in our 2 active rsfMRI studies and our ongoing task-based and rsfMRI study in adults with SCI and neuropathic pain.

Structural Preprocessing: We will perform preprocessing using the latest containerized fMRI preprocessing pipeline (FMRIPREP) version with standardized Brain Imaging Data Structure (BIDS) formatted Neuroimaging Informatics Technology Initiative (NIFTI) data. Each T1-weighted (T1w) volume will be corrected for intensity non-uniformity (INU) using N4BiasFieldCorrection and skull-stripped using antsBrainExtraction.sh (using the OASIS template). Brain surfaces will be reconstructed using recon-all from FreeSurfer, and the brain mask estimated will be refined with a custom variation of the method to reconcile Advanced Normalization Tools (ANTs)-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle. Spatial normalization to the International Consortium for Brain Mapping (ICBM) 152 Nonlinear Asymmetrical template will be performed through non-linear registration with the Registration tool of ANTs using brain-extracted versions of T1w volume and template.

fMRI Preprocessing: We will perform preprocessing with the latest

containerized FMRIPREP85 version with standardized BIDS formatted NIFTI data. Functional data will be slice time corrected using 3dTshift from Analysis of Functional NeuroImages (AFNI) and motion corrected using mcflirt. This is followed by co-registration to the corresponding T1w using boundary-based registration with 9 degrees of freedom, using bbregister (FreeSurfer). Motion correcting transformations, field distortion correcting warp, BOLD-to-T1w transformation and T1w-to-template (Montreal Neurological Institute, MNI) warp will be concatenated and applied in a single step using antsApplyTransforms (ANTs v2.1.0) using Lanczos interpolation. Physiological noise regressors will be extracted by applying CompCor. Principal components will be estimated for the two CompCor variants: temporal (tCompCor) and anatomical (aCompCor). Framewise displacement and DVARS90 will be calculated for each functional run using the implementation of Nipype. Independent Component Analysis (ICA)-based Automatic Removal Of Motion Artifacts (AROMA) will be used to generate aggressive noise regressors and to create a variant of data that is non-aggressively denoised.

For Aim 3, we will analyze miRNA expression profiles for raw cycle threshold (Ct) values using real-time Statminer software (Integromics, Inc) to identify significantly altered miRNAs. For relative quantification of miRNAs between placebo and brivaracetam-treated samples, the following steps will be performed in the Statminer software suite: quality control of biological replicates, filtering of miRNAs expression having Ct values below cycles and the detection of expression in all biological replicates of calibrator and target. Statistically significant miRNAs will be selected based on stringent parameters such as Benjamin-Hochberg FDR and data will be conservatively selected with adjusted p-values and p-value lower than 0.01 and 0.05, respectively. Functional pathway analysis of altered miRNAs and their association with genes related to reduction in neuropathic pain will be performed using Ingenuity Pathway Analysis (IPA) program (Ingenuity Systems Inc., Redwood City, CA). For clinical correlation analysis, data comparing changes in miRNA expression will be described as means with standard error of the mean. To analyze the differences between group means we will use analysis of variance after assessing for distribution and variance. We will use Games-Howell test for multiple comparisons.

*15.2* Power Analysis:

We present power and sample size analysis for the primary endpoint; a 2-point improvement in neuropathic pain intensity as assessed by the

International Spinal Cord Injury Pain Basic Dataset. We based our sample size calculation on variations in pain intensity observed in an ongoing clinical trial (DoD W81XWH-14-SCIRP-CTA, Morse PI). In this sample, average neuropathic pain intensity in 28 adults with SCI was 3.43+3.17. Based on this, a sample size of 20 per arm will have more than 80% power to detect a significant difference in pre-post changes of neurological pain between the two arms at a two-sided significance α level of 0.05. This sample size is sufficient to address the exploratory analyses proposed in Aims 2-3.

*15.3* Statistical Analysis:

All statistical analyses will be conducted with Stata v. 1771 or SAS v.9.472 assuming a 5% level of significance unless otherwise stated. Participant characteristics will be described using frequency counts and percentages (nominal variables) and means/standard deviations (SDs) or medians and interquartile ranges (IQRs) (continuous variables). Chi-square tests and t-tests or rank-sum tests will be used to compare the subject characteristics between the treatment arms.

<u>Aim 2 statistical analysis</u>

FMRI data will be processed using the conn functional connectivity toolbox with established standardized controls for multiple comparisons (SPM family wise error correction methods). Data will undergo realignment, scrubbing, artifact detection, and CompCor denoising. Primary analyses will focus on OP1/OP4 and insula regions-of-interest for resting-state connectivity and exploratory multivariate pattern analyses. Task-based fMRI will undergo the same preprocessing pipeline and will be modeled with a general linear model. Within-group pre-post changes in task-based brain activation and resting-state connectivity will be tested using paired t-tests or Wilcoxon signed-rank tests.

Between-group differences of pre-post changes in these measures will be tested using 2 sample t-tests or Mann-Whitney U tests. Mixed effects models with correlated errors will also be used to test the effect of CMR on brain imaging outcomes after adjusting for potential confounders, which will include the subject-level effect, time, group indicator, and time-by-group interaction as predictors, and age, race, and other covariates as appropriate. We will use False Discovery Rate (FDR) correction to control for the overall Type 1 errors for the voxel-level analyses. We will test the correlation between changes in brain function and clinical measures of sensory and

motor function using Pearson's correlations coefficients with 95% confidence interval calculated based on Fisher's Z transform.

*15.4* Data Integrity:

Study staff will collect and store data. Data will be collected electronically or on paper forms. All electronic data will be stored on Box Secure Storage or REDCap. Paper forms will only be accessible by the study staff, trained study coordinator, and the principal investigator. All paper documents will be kept in locked file cabinets in locked offices at all times. Participant names, contact information, health history, and other information that can be traced back to the participant will be kept separately from data collected for the study. Personal information will be kept in a locked office and away from data or in a separate folder on Box Secure Storage. Protocol sheets used during data collection will only have the participant's ID.

Data integrity of the data acquisition will be tested at the time of acquisition. Both the MRI technician and the PI or study staff will be present to monitor the data in real life.

All study records will be kept indefinitely after the study is closed. Research records will be stored in a manner to protect the confidentiality of participant information.

Drs. Battaglino and Morse will review data monthly. They will be responsible for monitoring the completeness of all data and source documents as well as monitoring the informed consent procedures. Checklists and note pages are used to note any deviations or omissions from the protocols. Any deviation to the protocol that may have an effect on the safety or rights of the volunteer, or the integrity of the study will be promptly reported to the IRB.

## 16.0 Health Information and Privacy Compliance

*16.1* Select which of the following is applicable to your research:

☐ My research does not require access to individual health information.

☒ I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research:

Identify the source of Private Health Information you will be using for your research (Check all that apply)

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

☒ I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☒ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☒ Other. Describe:

A screening phone survey to determine eligibility will be completed and stored in paper format and/or in REDCap. After consent, a health survey will be collected in paper format and stored in the participants study file.

*16.2* Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.

The team will access PHI for screening purposes according to institutional policies. The team will access and record PHI for data collection only after receiving permission from each enrolled study participant.

*16.3* Approximate number of records required for review: 60

*16.4* Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

☒ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.
We will conduct prescreening over the phone or in person in a private setting. We will communicate regarding scheduling and other important study information via phone, text, Zoom for Healthcare, email, or written communication, based on participant preference. Our communication plan will be clearly presented in the consent form.

*16.5* Explain how the research team has legitimate access to patients/potential participants:

Each site's PI and team will cover recruitment from all outpatient locations within their geographical catchment area. Only individuals who have opted in for research contact will be approached.

Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☐ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☒ In REDCap (recap.ahc.umn.edu)

☒ Store ☒ Analyze ☒ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☒ In OnCore (oncore.umn.edu)

☒ Store ☒ Analyze ☒ Share

☒ In the University's Box Secure Storage (box.umn.edu)

☒ Store ☒ Analyze ☒ Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

☐ Store ☐ Analyze ☐ Share

☒ In an AHC-IS supported desktop or laptop.

| Name | UMN Device # |
|---|---|
| Dr. Ricardo Battaglino | 20190593 |
| Nguyen Nguyen | 20230504 |
| Rob Wudlick | 20192649 |
| Brian DeVries | 20200957 |

☒ Other:

MSI (Minnesota SuperComputer Institute) to analyze the MRI Data in a secure way and share the data location in a secure way. This platform is needed because the MRI datafiles are very large. MRI data acquisition will not contain personal health information.

Indicate if data will be collected, downloaded, accessed, shared, or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive (“flash” or “thumb” drives) not previously listed

☐I will use a mobile device such as a tablet or smartphone not previously listed

*16.6* Consultants. Vendors. Third Parties: -

*LC Sciences*
We will send blood serum samples to LC Sciences (Houston, TX) to perform microRNA analysis (non-genomic analysis). LC Sciences will have access to de-identified data only.

*REDCap eConsent*
The informed consent form and HIPAA form will be signed with an eSignature using REDCap. The REDCap eConsent process is a 21 CFR Part 11 compliant method for electronic signature capture. For more information on REDCap compliance, please visit:
https://redcap.ahc.umn.edu/surveys/?s=3PT9FY73NC&topics___ec=1#ec

Links to identifiable data:
The research data will be collected on RedCap and on the MRI. Those data will not contain personal identifiable information. Only the PIs and designated study staff will have a document that links the name with the code, which will be kept secure on the University Box secure storage.

Sharing of Data with Research Team Members:
Only deidentified data will be shared with team members. The PIs and clinical trial coordinators will have access to identifiable information for contact purposes.
Storage and Disposal of Paper Documents:
Documents will be stored in a secure closet behind secure doors in the PI and Co-PI's offices and labs. Documents that need to be disposed will be disposed of in secure bins and then shredded.

## 17.0 Confidentiality

Data Security:
Clinical data will be stored on Research Electronic Data Capture (REDCap) and on HIPAA protected encrypted servers. Participant confidentiality will be safeguarded by password protected databases and locked file cabinets. Research records will be stripped of identifying information, with keys identifying participants available only to the PI or selected study-related personnel who have met the necessary Responsible Conduct of Research, HIPAA, human participants, data security and study specific training requirements. Brain imaging will be acquired via standardized protocols. Brain imaging will be acquired via standardized protocols. MRI data acquisition will not contain personal health information. The MRI data will be stored in digital form on encrypted servers.

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the participant is alive) at the end of their scheduled study period.

Procedures are in place for maintaining the full confidentiality of all information collected. Participant confidentiality will be protected by securing all hard copy study files in locked filing cabinets. Electronic files containing personal identifiers will be stored on Box Secure Storage or REDCap. All study staff receive training on privacy standards for maintaining participant confidentiality. All published reports will be of summary nature and no individual participants will be identified beyond the investigative staff involved in the project.

REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be housed on secure servers operated by the UMN Academic Health Center's Information Systems group (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the backups stored in accordance with the AHC-IS retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The AHC-IS servers provide a stable, secure, well-maintained, and high-capacity data storage environment, and both REDCap and MySQL are widely-used, powerful, reliable, well-supported systems. Access to the study's data in REDCap will be restricted to the members of the study team by username and password.

The informed consent form and HIPAA form will be signed with an eSignature using REDCap. The REDCap eConsent process is a 21 CFR Part 11 compliant method for electronic signature capture. For more information on REDCap compliance, please visit:
https://redcap.ahc.umn.edu/surveys/?s=3PT9FY73NC&topics___ec=1#ec

Data files will be stored locally at the UMN Department of Rehabilitation Medicine. All data are stored on a secure HIPAA protected PC, and on secure HIPAA protected servers (Box Secure Storage). Raw and processed brain imaging data are also stored by the biostatistician/brain imaging

analysis specialists responsible for brain analysis and are backed up weekly.

Training: All study staff will be appropriately trained in data security.

Authorization of access: Only designated IRB-approved staff will have access to the data.

Password protection/encryption/physical controls: All data will be stored in REDCap/Box.

Separation of Identifiers: Study staff will keep the mapping of identification code to the identity of the participant in a database protected by two-levels of password protection stored separately from the data on Box.

## 18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

*18.1* Data Integrity Monitoring.

This trial will be conducted in compliance with this protocol, good clinical practice, and the applicable regulatory requirements.

Study Oversight. Continuous study oversight will be provided by the study's PI, Dr. Ricardo Battaglino, Vice Chair of Research, Department of Rehabilitation Medicine, University of Minnesota (rbattagl@um.edu, 612-625-2661),Co-I, Dr. Scott Falci, Swedish Medical Center, and Co-I/study physician, Dr. Leslie Morse, University of Miami collaborator.

Plan for Data Management. Data will be collected electronically (imaging files) or on paper forms. All electronic data will be stored on Box Secure Storage or REDCap. Paper forms will only be accessible by the study staff, trained study coordinator, and the principal investigator. All these documents will be kept in locked file cabinets in locked offices at all times. Participant names, contact information, health history, and other information that can be traced back to the participant will be kept separately from data collected for the study. Protocol sheets used during data collection will only have the participant's ID.

MRI imaging data will be identified by study ID without personal identifiers and stored on the system drive behind the institutional firewall. All computers are password-protected and will only be used by trained study staff and for study purposes only.

All study records will be kept indefinitely after the study is closed. Research records will be stored in a manner to protect the confidentiality of participant information.

*18.2* Data Safety Monitoring

Plan for Monitoring Safety. The safety environment of UMN participants will be overseen and monitored by PI, Dr. Battaglino, Co-I, Dr. Scott Falci, and Co-I/study physician, Dr. Morse. We will monitor to assure that participants meet eligibility criteria; that the informed consent process is conducted appropriately, that the data will be collected and analyzed as specified in the protocol, that adverse events (defined below) are reviewed promptly and reported as required (detailed below), that dropouts are documented, and that primary and secondary endpoints are evaluated. According to the data safety-monitoring plan, study participation will be terminated immediately in the event of injury or increased morbidity (drug intolerance). Data and all procedures will be monitored at each measurement time point and monthly throughout the duration of the study to ensure the safety of participants.

We will establish a Data Safety and Monitoring Board (DSMB) in accordance with NIDILRR and FDA guidance for clinical trial sponsors. UMN's institutional CTSI will assist with identifying board members and assist with managing board activities. The DSMB will review safety and efficacy data following a recruitment pause after the first 20 participants are enrolled and will make recommendations regarding continuation or termination of the study. The DSMB will also meet and review safety data quarterly and as needed throughout the duration of the study. The safety environment of all participants will be overseen and monitored by Dr. Morse (study Co-I). We will monitor to assure that participants meet eligibility criteria; that the informed consent process is conducted appropriately, that the data will be collected and analyzed as specified in the protocol, that adverse events are reviewed promptly and reported as required, that dropouts are documented, and that primary and secondary endpoints are evaluated. Data and all procedures will be monitored at each measurement time point and monthly throughout the duration of the study to ensure the safety of participants.

Unblinded Study Physician/Medical Monitor. Our safety monitoring plan also includes an independent medical monitor: Dr. Michael Stillman (Thomas Jefferson University). Dr. Stillman will review all reported adverse events on a monthly basis and as needed with the PI, Dr. Battaglino and study physician, Dr. Morse, who will inform Dr. Stillman immediately of all study-related unanticipated problems involving risk to volunteers or others, serious adverse events, and all volunteer deaths associated with the

protocol, and provide an unbiased written report of the event to the IRB and FDA. The medical monitor will comment on the outcomes of the event or problem, and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor will also indicate whether he concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation, and reports of events resulting in death will be promptly forwarded to the IRB and FDA.

Reporting Adverse Events. Anticipated adverse events (detailed above in 13.0, Risks to Participants) will be identified while interviewing participants, during physical exams, and while reviewing laboratory results. Participants also will be directed to call study staff to report adverse events that may occur between these visits. All adverse events will be noted on the Adverse Events log form that will be kept in the participant's file. Unanticipated adverse events and unanticipated serious adverse events (as defined in CFR Title 21), also will be identified during testing time points and through participant self-reporting between these visits. They will be noted on the Adverse Events Log and promptly brought to the attention of the study PI and study physician.

Unanticipated serious adverse events will be reported within 5 working days to the IRB as required.

Follow-up of Adverse Events. In the unlikely event that a participant is injured as a result of this research study, medical care, including emergency treatment will be provided.

Assessment of Risk. This is a moderate risk pilot clinical study. As such, our safety monitoring plan will include a medical monitor: Dr. Michael Stillman. Drs. Battaglino and Morse will review all reported adverse events on a monthly basis with Dr. Stillman, the medical monitor. Additionally, Drs. Battaglino and Morse will inform Dr. Stillman immediately of all study-related unanticipated problems involving risk to volunteers or others, serious adverse events, and all volunteer deaths associated with the protocol, and provide an unbiased written report of the event to the IRB. The medical monitor will comment on the outcomes of the event or problem, and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor will also indicate whether he concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation, and reports of events resulting in death will be promptly forwarded to the IRB.

## 19.0 Provisions to Protect the Privacy Interests of Participants

Protecting Privacy:

Study staff will receive HIPAA and data security training to maintain participant confidentiality prior to the initiation of participant recruitment. Non-identifiable research related data will be directly entered by participants into REDCap. REDCap is a secure, web-based application designed to support data capture for research studies. Trained staff will double enter data from de-identified case report forms containing variables collected on questionnaires. All paper form files with personal identifiable information will be stored in locked filing cabinets. Electronic files containing personal identifiers will be stored on Box Secure Storage and REDCap. In the instance that participants engage in a study-related videoconference through the Zoom video-conferencing platform, Zoom does not have access to identifiable protected health information, and they protect and encrypt all audio, video, and screen-sharing data. Zoom sessions will not be recorded or maintained. All study staff will receive training on privacy standards for maintaining participant confidentiality. The informed consent form and the HIPAA form will be signed with eSignature using a REDCap form that is compliant with FDA Title 21 CFR Part 11. For more information on REDCap compliance, please visit: https://redcap.ahc.umn.edu/surveys/?s=3PT9FY73NC&topics___ec=1#ec

Procedures are in place for maintaining the full confidentiality of all information collected. Participant confidentiality will be protected by securing all hard copy study files in locked filing cabinets. Electronic files containing personal identifiers will be stored on Box Secure Storage or REDCap. All study staff receive training on privacy standards for maintaining participant confidentiality. All published reports will be of summary nature and no individual participants will be identified beyond the investigative staff involved in the project.

Access to Participants*:*

Participants have been fully informed of the ways in which their data will/may be used during the informed consent process. The research team has been trained in conducting these conversations and the participants are also assessed for their understanding of consent prior to signing the consent form or initiating any study procedures.

## 20.0 Compensation for Research-Related Injury

Compensation for Research-Related Injury:

In the unlikely event that a participant is injured as a result of this research study, medical care, including emergency treatment will be provided. The participant's insurance company may be billed for treatment.

Contract Language: N/A

## 21.0 Consent Process

*21.1* Consent Process (when consent will be obtained):

Informed consent will be obtained by study staff electronically via REDCap, in person at the enrolling site, or a location convenient to the participant by study. For participants who meet the inclusion criteria, a qualified member of the study team will follow the informed consent process over Zoom, and the participant will provide consent through the REDCap eConsent form. Prior to obtaining consent, all participants will be given ample time to read the consent form and encouraged to ask questions. Potential participants will be reminded that participation is strictly voluntary and will not affect their current or future care at the enrolling site or any affiliated institute. Each participant will be told that they will be free to discontinue participation at any time, but that discontinuation of the drug must be done under medical supervision to ensure it is done safely. A copy of the signed informed consent form will be sent or given to the participant. Participants will be provided with Dr. Battaglino's contact information if questions should arise during the course of the trial. Consent will be obtained only from the participant and we will not seek consent from legally authorized representatives. We will not enroll any participants unable to give consent due to altered mental capacity. We will not enroll children therefore will not obtain assent.

*21.2* Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

*21.3* Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): N/A

*21.4* Non-English speaking Participants:

We will include enrollment of non-English speaking participants. We will provide a translator to interpret consent forms. The interpreters are trained and required to protect participant privacy. Additionally, PI Dr. Battaglino will also be available as needed to carry out study procedures in Spanish, correspond with Spanish-speaking participants, and provide Spanish-English translation.

*21.5* Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): N/A

*21.6* Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

*21.7* Adults Unable to Consent: N/A

- Permission: N/A
- Assent: N/A
- Dissent: N/A

## 22.0 Setting

Research Sites:
University of Minnesota, Minneapolis, MN
Mayo Clinic, Rochester, MN
Regions Hospital, Saint Paul, MN
Courage Kenny Rehabilitation Institute, Minneapolis, MN

## 23.0 Multi-Site Research

Study-Wide Recruitment Methods:
Sites will draw on their clinical and community networks for recruitment, utilizing flyers and recruitment cards.

Study-Wide Recruitment Materials:
Recruitment flyers and cards will facilitate recruitment efforts.

Communication Among Sites:
Investigators, study coordinators, data managers, and data collectors from each site will have monthly or as needed calls to discuss matters of this study. Sites may contact other sites. Communication may be by phone, email, in person, fax, in person, or other forms of correspondence.

Communication to Sites:

Investigators, study coordinators, data managers, and data collectors from each site will have monthly or as needed calls to discuss matters of this consortium and this study. Sites may contact other sites. Communication may be in phone, email, in person, fax, in person, or other forms of correspondence.

## 24.0 Coordinating Center Research: N/A

## 25.0 Resources Available

Resources Available:

Overview of MN Regional SCIMS Resources. Located within the rich scientific milieu of Minnesota's "Medical Alley," our research program leverages world-class research infrastructure, core facilities, and one of the leading technology commercialization offices in the country. We will draw on this rich scientific environment to contribute to the national database, complete our proposed site-specific and module projects, and contribute to module projects proposed by collaborating Model System centers. UMN ranks ninth among public universities in research spending, with more than $950 million in research expenditures in fiscal year 2019 and research awards of more than $860 million. Blue Ridge ranked the UMN Department of Rehabilitation Medicine fifth nationally based on NIH funding in 2020. At Mayo Clinic, total research and education funding in 2018 exceeded $1.1 billion. In 2018, Mayo Clinic's research programs generated 12,760 active IRB-approved studies: 3,067 new human research studies, 5,268 active grants and contracts, and 9,725 research and review articles in peer-reviewed journals.

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