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*	

☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;** **These groups each have their own application process.**
☒ **Yes** ☐ **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** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu*	
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
☒ **Yes** ☐ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol. Contact: privacy@umn.edu*	
☐ **Yes** ☒ **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.**

		Contact: ics@umn.edu	**These groups do not have a separate application process but additional information from the study team may be required.**
☐ **Yes** ☒ **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** ☒ **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** ☐ **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*	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff Contact: oncore@umn.edu*	**Does not affect IRB approval.**

PROTOCOL COVER PAGE

Protocol Title	Brivaracetam to Reduce Neuropathic Pain in Chronic SCI: A Pilot Clinical Trial
Principal Investigator/Faculty Advisor	Name: Dr. Ricardo Battaglino
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IND/IDE # (if applicable)	150388
IND/IDE Holder	Leslie Morse
Investigational Drug Services # (if applicable)	NA
Version Number/Date:	Version: 8.0 / Date: 03/18/2024

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
2.0	11/1/2021	• Increased medical clearance window • Add ancillary reviews • Add labwork, INR • Adding Study Specific Webpage • Adding EPIC medical record review • Clarified inclusion criteria • Adding new recruitment strategies • Changing monthly check ins to weekly • Add DN4 assessment tool	Yes
3.0	01/25/2022	• Allow for virtual participation • Allow for paper or electronic consent • Add off-campus option for end of study labs • End of study testing to occur prior to drug ramp down • Uniform formatting throughout document • Included previously added assessment tools description	Yes
4.0	05/16/2022	• Clarifying protocol is multi-center pilot clinical trial (UMN, local site, and Swedish Medical Center/Craig Hospital, additional site) • Clarifying drug dosage and handling • Consent form updated to state Co-I COI.	Yes

Revision #	Version Date	Summary of Changes	Consent Change?
4.1	06/06/2022	• Uniform compensation information described in consent form	Yes
5.0	08/11/2022	• Adding recruitment method with MyChart announcements • Removed Rebekah Summers listed device • Added Brian Devries listed device	
6.0	09/22/2022	• Adding Visit 4 with Long-term follow up measures (1-month post medication cessation) -CHART-SF -PHQ-9 -DN4 -ISCI Pain Basic Data Set -BPI -PCS -Penn SFS -TSK -PSQI -Satisfaction with Life -Moorong SES -PDI	Yes
6.1	09/26/2022	• Adding $50 additional payment for Visit 4	Yes
7.0	06/20/2023	• Clarifying Section 18 to state that CTSI provides further monitoring for this study	No
8.0	03/18/2024	• Revise Ricardo Battaglino as Principal Investigator • Revise Leslie Morse as Co-I, University of Miami collaborator	No (completed enrollment)

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

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:

SCI is associated with severe neuropathic pain that is often refractory to all pharmacological intervention. Our preliminary data suggest brivaracetam is a mechanism-based pharmacological intervention for neuropathic pain in SCI. In this project we will conduct a randomized, placebo-controlled pilot clinical trial to assess feasibility of a 3-month treatment course with brivaracetam. We will assess changes in pain intensity and periaqueductal gray hyperactivity. We will assess baseline periaqueductal gray hyperactivity and microRNA levels as potential biomarkers of response to treatment. We will use these preliminary findings to design larger clinical trials to establish efficacy of brivaracetam to treat neuropathic pain in SCI. The pilot data are necessary to adequately power the larger clinical trial based on SCI-specific data for each outcome of interest. Here we will be able to present the scientific evidence base supporting the rationale for this project.

Specific Aims:

1. Specific Aim 1: Determine whether a 3-month course of daily brivaracetam is safe and effective at reducing severe below-level neuropathic pain after SCI.
2. Specific Aim 2: Determine whether a 3-month course of daily brivaracetam decreases periaqueductal gray activity in SCI.
3. Specific Aim 3: Determine whether baseline microRNA levels are associated with response to brivaracetam treatment.

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 to establish drug efficacy and validate novel predictive biomarkers of response to therapy.

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 with corresponding reduction in periaqueductal gray brain activity by rsfMRI (Aim 1). We also hypothesize that either periaqueductal gray brain activity or circulating miRNA-485 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 (J Neurosurgery Spine 2002, 2018).

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 (see appendix, J Neurosurgery Spine 2002, 2018). With 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, 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

3.1 Primary Endpoint/Event/Outcome:

Our primary endpoints will be 1) safety as determined by number of drug related adverse events and assessed through weekly adverse event screening by phone, and 2) efficacy as determined by reduction in pain intensity assessed by the Brief Pain Inventory. We will use the clinically meaningful reduction in Brief Pain Inventory score of 1 point or more as the definition of "drug response" in this study.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

Secondary outcomes include brain resting state functional connectivity and various psychosocial factors related to participants' experiences with SCI, such as change in mood, satisfaction with life, and community integration.

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

4.1 Description:

Intervention: brivaracetam or placebo administration. Because this is an off-label use of an FDA approved drug, we received an Investigational New Drug (IND) designation from the FDA for this study (IND Holder Morse, #150388). RxArtisans Pharmacy (Wayzata, MN) will FedEx the drug to the participant directly or to the Rehabilitation Department Boynton Bridge, University of Minnesota (UMN) for distribution, and study staff will send an email notification that the drug has been sent by overnight mail. To minimize wasting of drug, RxArtisans will dispense and ship prescriptions for participants concurrent with the ramp-up schedule (weekly, biweekly, or as requested by study doctor). Once maximum dose is stabilized, RxArtisans will dispense and ship prescriptions monthly. 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 X 2 weeks followed by 50mg TID X 2 weeks followed by 100mg BID X for 48 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.

In the case of intolerance at 50mg BID during dose escalation, the dose will be reduced to 25mg daily or 25mg BID. In the case of intolerance, the dose will be reduced down 1 step to last tolerated dose. For intolerance at 100mg BID, the dose will be reduced to 50mg TID. For intolerance at 50mg TID, the dose will be reduced to 50mg BID. A dose of 50mg BID or higher must be maintained to complete the trial.

Drug discontinuation at study completion will be done according to the following protocol we use clinically that will be initiated for 2 weeks after end of study testing: Reduction to 50mg BID X 1 week followed by 50mg daily X 1 week. For those at the highest study tolerated dose of 50mg BID, the dose will be reduced to 50mg daily X 1 week and then stopped. At the end of study participants will be asked to mail empty bottles for pill counts with self-addressed and prepaid packaging, and will review the medication diaries via phone. We will use the clinically meaningful reduction in Brief Pain Inventory score of 1 point or more as the definition of "drug response" in this study. University of Minnesota Investigational Drug Services (IDS) will register the study, while Rx Artisans will be dispensing the drug.

4.2 Drug/Device Handling:

Brivaracetam or placebo will be compounded and dispensed by Rx Artisans 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 (25mg Purple, 50mg Green, 100mg Blue) 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 form including email, text, etc.) that the drug was received.

4.3 Biosafety: N/A

4.4 Stem Cells: N/A

4.5 Fetal Tissue: N/A

5.0 Procedures Involved

5.1 Study Design:

This is a multi-center randomized, double-blinded placebo-controlled pilot clinical trial. Each site (Swedish Medical Center/Craig Hospital, UMN) will enroll and study 20 adults, 18 years of age and older with SCI. Dr. Ricardo Battaglino will serve as PI, and Dr. Leslie Morse will serve as Co-I at UMN (local site). MRI data analysis will be conducted by Dr. Clas Linnman (Harvard University). Dr. Linnman will receive a deidentified dataset and will have no human subject interactions. Research activities at the Swedish Medical Center/Craig Hospital will be conducted under a separate IRB protocol at Craig Hospital.

Participants who meet the eligibility criteria will be randomly assigned to active drug (escalating brivaracetam dose to 100 mg twice daily for 3 months) or placebo based on a randomization schedule developed by our biostatistician. This is a simple computer generated 1:1 scheme that randomly assigns participants to arm A or arm B. Study participants, research coordinators, and study personnel involved in outcomes assessments and analyses will all be blinded. 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 pharmacies (RxArtisans). We have registered this pilot study with National Institutes of Health (NIH) clinical trials registry, www.clinicaltrials.gov (NCT04379011). The pilot data generated by this effort will be used to power a subsequent multi-center clinical trial.

5.2 Study Procedures:

<u>Overview of study procedures/study interventions.</u> All interventions and activities are summarized in Table 1 below and then described in detail in the subsequent text. Potential participants will undergo an initial screening for eligibility based on the criteria below. After giving informed consent, participants will be randomized. Eligible participants will be required to receive medical clearance from their primary care provider within one month of (prior to) the baseline appointment, including physical exam, health history, and lab work to confirm normal renal function, absence of liver cirrhosis, and absence of pregnancy.

Baseline testing includes a focused physical exam, mental health and health history, blood samples for batch analysis, and an MRI scan. These procedures can either take place 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. For participants who prefer not to undergo a research MRI, the MRI will be optional. Research blood banking will also be optional.

Participants must see their primary care physician to determine if they are eligible to enroll in this study, including having their physician order lab work to confirm that they are not pregnant (for females/people of childbearing potential) and that their kidneys and liver function properly. Their insurance will be charged and they will be responsible for any associated copays or costs. The study drug, research banking lab, baseline and end-of-study physical examinations, and MRIs performed by the study will be paid for by the study.

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.

CDE-recommended questionnaires relating to pain, mood, active suicidality, satisfaction with life, kinesiophobia, sleep quality, and community integration will be administered. Participants will then begin 3 months of active treatment (100 mg BID) or placebo. All participants will receive a medication diary to track study drug compliance and to record medication use. Blinded data collectors will perform weekly check-in calls to assess for medication-related adverse events including the PHQ-9 for changes in mood and suicidality. Reported AEs identified in these calls will be documented and immediately shared with the PI for review.

End of study assessments will be repeated 3 months after baseline testing and again 1 month after cessation of study medication (active/placebo). Lab work will be repeated to confirm normal renal function, absence of liver cirrhosis, and absence of pregnancy in individuals of childbearing potential at the end of the study. Specimen collection and analysis will either occur at the Fairview Clinical Research Unit or with the participant's

primary care provider, based on participant preference. Participants will receive $150 after baseline testing, $150 after end of study testing sessions and $50 after the 1-month post drug cessation follow-up to compensate them for their time and to assist with transportation.

Our primary endpoints will be safety (# of drug related adverse events) and efficacy (reduction in pain intensity assessed by the Brief Pain Inventory). We will use the clinically meaningful reduction in Brief Pain Inventory score of 1 point or more as the definition of "drug response" in this study. Secondary outcomes include change in mood, satisfaction with life, community integration, and brain resting state functional connectivity. All fMRI data will be deidentified and sent by secure server to Harvard Medical School for analysis by Dr. Linnman (consultant) as is done in our ongoing collaborative studies (Effects of Ekso-assisted gait training on Bone Health and Quality of Life: A Randomized Clinical Trial, PI Morse).

Suicide Protocol: Endorsement of active suicidality on PHQ-9 will trigger the suicide protocol. 911 will be called 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.

Modified Brief Pain Inventory (BPI) – main outcome. 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 VAS Pain 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 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].

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 1-10

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.

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 simple Likert scale.

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.

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.

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

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.

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

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 Cortical Activity by Brain MRI. MRI scans of the brain will be performed for participants who are eligible and provide consent to MRI. Testing will be performed at baseline and end of study. We will use 3 Tesla Magnetic Resonance Imaging to collect i) brain structure (Multi Echo Magnetization Prepared Rapid Acquisition Gradient Echo, MEMPRAGE) ii) brain white matter integrity (Diffusion Weighted Imaging, DWI), iii) brain resting state functional connectivity (resting state functional Magnetic Resonance Imaging, rsfMRI), and iv) evoked responses to Motor Imagery

(MI). MI involves asking individuals to envision themselves executing motor actions, without actual execution, a task that activates the same or similar neural systems as the actual execution of motor actions.

Limited safety labs for hepatic cirrhosis, renal insufficiency, and pregnancy. At the final study visit, participants will complete a fasting blood draw either at the Clinical Research Unit or through their primary care provider. 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. INR will be collected at the discretion of the participant's primary care provider if the participant is on anticoagulation or has abnormal LFTs. 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 the study staff by the CRU staff.

Table 1. Study Procedures

Study Task	Pre-Screen	Visit 1*	Visit 2*	Visits 3 (end of study testing)	2 weeks drug dose reduction (after end of study testing)	Visit 4 (long-term follow-up)
Pre-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, surveys		X		X		x
Initiate intervention			X			
Dispense 3-month drug supply			X			
Reminder check-in: begin 2-week drug dose reduction protocol after end of study testing					X	
Limited safety labs (blood draw, required)				X		
Pill count/medication diary review					X	
Pregnancy test (for women of child-bearing potential)				X		
Adverse Events	Assessed weekly (phone)					

*Visits 1 and 2 may be combined for participant convenience

**Medical clearance must be clinically obtained from participants' primary care provider or other healthcare provider within 1 month prior to visit 1

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.

5.3 Study Duration:

This is a 2-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 2. Individual participant's participation will approximately be three months 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.

5.4 Use of radiation*: N/A*

5.5 Use of Center for Magnetic Resonance Research*:*

All participants who consent to MRI testing will get a 3T structural and functional MRI scan at baseline and after completion of the 3-month treatment course. The scanning protocol will be standardized between the two testing sites. We will collect i) brain structure (Multi Echo Magnetization Prepared Rapid Acquisition Gradient Echo, MEMPRAGE) ii) brain white matter integrity (Diffusion Weighted Imaging, DWI), iii) brain resting state functional connectivity (resting state functional Magnetic Resonance Imaging, rsfMRI), and iv) evoked responses to Motor Imagery (MI). MI involves asking individuals to envision themselves executing motor actions, without actual execution, a task that activates the same or similar neural systems as the actual execution of motor actions.

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 in the Fairview Clinical Research Unit (CRU), 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, quantitative proprioceptive recordings, standardized patient-rated questionnaires will be stored on Research Electronic Data Capture (REDCap) and on encrypted servers.
Imaging of brain activation (fMRI), and brain networks via functional resting-state (functional connectivity), and task-based (effective connectivity) 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, then the de-identified xls 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: N/A

8.0 Study Population

8.1 Inclusion Criteria:

- 18 years of age or older
- Completed inpatient rehabilitation and living in the community
- Ongoing severe below-level neuropathic pain (daily average 9/10 or 10/10)
- Tried and failed to achieve adequate pain relief with the use of other drugs (previous pain management drugs failed to decrease their pain below a self-reported level of 9 out of 10)

- 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).

8.2 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
- 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

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.

8.3 Screening:

A prescreening checklist will be administered to confirm basic eligibility prior to consenting. This includes confirming age, pain level, medication use, implanted medical devices or retained metal fragments, and other medical conditions. 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 and completing a physical exam and health history. The participant's insurance will be charged and they will be responsible for any associated copays or costs.

The participant's provider will provide UMN research staff with results via fax or email, or the participant may carry a hard copy. If the participant is a patient of Fairview, their medical records will be accessed directly by research staff who have obtained approval via the non-Fairview employed research staff (NERS) application process for conducting research tasks in Fairview facilities and systems.

Screening for hepatic cirrhosis, renal insufficiency, and pregnancy. Brivaracetam treatment is not safe for those who are pregnant, have hepatic cirrhosis, or kidney dysfunction. Therefore, in order 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. INR will be collected at the discretion of the participant's primary care provider if the participant is on anticoagulation or has abnormal LFTs. The blood lab report and medical clearance form will be faxed from the medical provider to the study coordinator within one month of draw. 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 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

9.1 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	Included/Allowed to Participate

social goods and services such as income, housing, or healthcare.	
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

9.2 Additional Safeguards:

This project aims to research an intervention that may help vulnerable adults with spinal cord injuries with severe neuropathic pain, a severe health condition, and non-English speakers. 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 proposed 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 consent 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

10.1 Local Number of Participants to be Consented:

30 participants are expected to be screened. 20 participants will be enrolled at UMN.

11.0 Local Recruitment Methods

11.1 Recruitment Process:

We anticipate screening 30 individuals with SCI to recruit and enroll 20 participants. 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 (www.z.umn.edu/SCIPain). 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 the Co-Principal Investigators from among 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. The patient will be given the choice, if interested, to be approached by the investigator in person, over phone or e-mail or have them reach out to the investigator. A flier or recruitment card about the study may be sent to potential participants, asking them to contact the study coordinator if they are interested.

Individuals who respond to the recruitment materials will be taken through a phone screening questionnaire with the study coordinator. If following the phone screen, the potential participant is eligible and interested; the study coordinator will schedule the screening study visit.

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 not limited to Get Up Stand Up to Cure Paralysis, Minnesota Spinal Cord Injury Association, and Morton Cure Paralysis.

MN SCI Model System Members: Like above, participants may be told about this clinical trial by their clinicians and other personnel at healthcare centers (MHealth/Fairview, Allina Health Courage Kenny Rehabilitation Institute and HealthPartners/ Regions Hospital, Hennepin Healthcare, and Mayo Clinic) that specialize in the care and wellbeing of individuals with SCI.

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 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 Mailings: We will work with Fairview Research Recruitment Services to identify individuals with SCI in the overall MHealth Fairview Healthcare system and send recruitment MyChart announcements and recruitment mailings through the mail, pending approval from the Fairview Research Administration. Patients of Dr. Morse will be pre-screened using their medical chart and sent a letter in the mail if they meet eligibility criteria. Patients who have opted out of having their records used for research will not be included.

11.2 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. A study coordinator will contact individuals for 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 principal investigator and co-investigator (Dr. Ricardo Battaglino and Leslie Morse) and their team from among patients under Dr. Morse 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.

Through BPIC involvement EPIC will be searched on the hits provided by BPIC. If eligible a mailing will be sent out.

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).

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

11.4 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 1-month follow up testing (Visit 4).

12.0 Withdrawal of Participants

12.1 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
- 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

12.2 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.

12.3 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

13.1 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 are 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 the study coordinator, or an investigator regarding any side effects or adverse events that occur.

MRI risks

There are minimal risks or side effects of MRI testing for participants who do not have medical devices or implants. These risks include magnetic objects being turned into projectiles by the MRI, claustrophobia in the scanner, and hearing damage if hearing protection is not worn in the scanner.

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 at the UMN in the Fairview Clinical Research Unit (CRU), 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 secure and locked space with 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 code number 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 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').

13.2 Reproduction Risks:

Pregnancy
We are excluding pregnant or lactating people from this study.

13.3 Risks to Others: N/A

14.0 Potential Benefits to Participants

14.1 Potential Benefits:

Because this study will be used to develop clinical trials 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 main outcome variables of interest include various dimensions of pain, mood (PHQ-9), life satisfaction (SWLS), resting state brain connectivity, and community integration (CHART-SF) measured at baseline and again at 3-months of treatment. Of particular interest is whether there is a difference in pain reduction from baseline to end of study between the treatment and control groups; this will be analyzed in this pilot with linear regression including terms for group and time and the interaction of group by time. We note that many of these instruments have bounded scores and we will include analyses that recognize these (via, e.g., non- linearities or recognize the bounds such as Tobit regression) Further exploratory analyses will examine the relationships (correlations) between changes in pain and changes in mood, life satisfaction, resting state brain connectivity, and community integration using linear regression.

For aim 2, we will use the same analytic approach we have refined in our 2 active rsfMRI studies. MRI data will be analyzed using the SPM12 based Conn toolbox 3 (Version 17f, Matlab R2018b). Preprocessing steps include 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 include scrubbing, aCompCor, ICA-based denoising, Global Regression, and 0.008 to 0.09 Hz band-pass filtering). Three main comparisons will be evaluated: The effect of drug treatment on rsfMRI measures, the effect of pain intensity on rsfMRI measures (each via linear regression as in Aim 1), and the differences in rsfMRI measures between active drug responders and non-responders; this last will also be analyzed via linear regression; note, however, that this will be limited to those in the active group and people in the placebo group will not be included. First, we will evaluate 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 will evaluate, on a voxel-by-voxel basis, amplitude of low frequency fluctuations (ALFF) and intrinsic resting state functional connectivity.

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 false discovery rate (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 proteins related to reduction in neuropathic pain will be performed using Ingenuity Pathway Analysis (IPA) program (Ingenuity Systems Inc., Redwood City, CA). This software compiles known interactions for relevant miRNAs potential/ targets from published literature. This does not involve detection of genotypes, mutations, or chromosomal changes. For clinical correlation analysis, data comparing changes in miRNA expression will be described as means with standard error of the mean. In order to analyze the differences between group means we will use analysis of variance (ANOVA) after the assessing for distribution and variance. Multiple comparisons will be performed using Games-Howell test.

15.2 Power Analysis:

Part of the goal of this pilot study is to obtain information that can be used for formal sample size estimation, including effect sizes and standard error estimates; therefore, analyses are included here that may not be included in a non-pilot follow-up (including the randomization analyses described below); further, some of the analyses here are exploratory to help in the design of a follow-up study. Also, (1) robust standard errors will be used in all cases to help guard against the effects of heteroskedasticity; (2) although there are a number of outcomes and, therefore, analyses, no adjustments for multiple comparisons will be made in this pilot study as the prime aim is not the level of statistical significance but rather the estimation of results needed for planning a follow-up. Of course, when disseminating our findings we will report the number of tests performed and the actual p-values so that readers can make their own adjustments if wanted.

15.3 Statistical Analysis:

All statistical analyses will be conducted with Stata v. 16 (Copyright 1985-2019 StataCorp LLC, College Station, TX) or SAS v.9.4 (Copyright (c) 2002-2012 by SAS Institute Inc., Cary, NC, USA) 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 participant characteristics between the treatment arms.

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. Collected data will have the participant's identification code and some computer software used to collect data will have the date and time marked on the file. Protocol sheets used during data collection will only have the participant's ID.

Imaging data (MRI scan results) will be identified by study ID without personal identifiers and stored on the system drive behind the institutional firewall or on Box Secure Storage. Some institutions consider MRI of the brain to contain identifiers due to the presence of facial features. We will not use software to mask facial features, therefore identifiable MRI data will be shared with Dr. Linnman for analysis. 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.

Dr. Morse will review data monthly. She 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:

16.2 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 pre-screening phone survey will be completed and stored in paper format and REDCap to determine eligibility. After consent a health survey will be collected in paper format and stored in the participants study file.

16.3 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.

16.4 Approximate number of records required for review: 25

16.5 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. Our communication plan will be clearly presented in the consent form.

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

The PI and her team will cover recruitment from all outpatient locations within greater Minneapolis/Saint Paul area. We will also recruit with flyers and social media postings within the greater Minneapolis/Saint Paul area.

16.7 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
Dr. Leslie Morse	20160309, 20190592
Nguyen Nguyen	20190734
Rob Wudlick	20192649
Brian DeVries	20200957

☒ Other:

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

16.8 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

16.9 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 PI/Co-PI will have a document that links the name with the code, which will be kept secure on the University Box secure storage.

16.10 Sharing of Data with Research Team Members:
Only deidentified data will be shared with team members. The PI and clinical trial coordinator will have access to identifiable information for contact purposes.

16.11 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

17.1 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. MRI data acquisition will not contain personal health information. The MRI

data be stored in digital form behind institutional firewalls or on Box Secure Storage.

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. Further monitoring will be completed by a CTSI monitor that will be assigned to the study.

Study Oversight**.** Continuous study oversight will be provided by the study PIs, Dr. Falci, Swedish Medical Center/Craig Hospital site PI, and Drs. Ricardo Battaglino and Leslie Morse, UMN site PI and Co-I, Department of Rehabilitation Medicine, University of Minnesota.

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 of 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. Personal information will be kept in a locked office and away from data. Collected data will have the participant's identification code and some computer software used to collect data will have the date and time marked on the file. 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 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.

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. 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.

Unanticipated serious adverse events will be reported within 5 working days to the UMN 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. Dr. Morse will review all reported adverse events on a monthly basis with Dr. Stillman, the medical monitor. Additionally, Dr. 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

19.1 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.

19.2 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

20.1 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.

20.2 Contract Language: N/A

21.0 Consent Process

21.1 Consent Process (when consent will be obtained):

Informed consent will be obtained electronically via REDCap or in person at the CRU (or a location convenient to the participant) by study staff. 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 UMN or any affiliated institute. Each participant will be told that they will be free to discontinue participation in the experiment 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. Morse'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 English and Spanish speaking participants. We will provide a translator to interpreted consent forms. The interpreters are trained and required to protect participant privacy. Additionally, Co-I 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

22.1 Research Sites:

University of Minnesota, Minneapolis

- Department of Rehabilitation Medicine
- Health Clinical Research Unit, Phillips-Wangensteen Building

Craig Hospital/Swedish Medical Center, Englewood, CO

23.0 Multi-Site Research

23.1 Study-Wide Number of Participants:
20 enrolled participants. 30 screened participants.

23.2 Study-Wide Recruitment Methods:

We anticipate screening 30 individuals with SCI to recruit and enroll 20 participants across the 2 enrollment sites (Swedish Medical Center/Craig Hospital and University of Minnesota). The PI (Swedish Medical Center/Craig Hospital site) sees over 50 patients a year with severe sublesional neuropathic pain. Therefore, at Swedish Medical Center/Craig Hospital we will recruit potential participants from his clinical practice. The Department of Rehabilitation Medicine houses an ACGME-accredited, 12-month SCI Medicine Fellowship program. This fellowship leverages collaborative relationships with all specialty hospitals in the greater Minneapolis area providing acute inpatient rehabilitation for spinal cord injury, including Fairview Acute Inpatient Center, Minneapolis VA Medical Center, Regions Hospital, and Courage Kenny Rehabilitation Institute. Therefore, we will recruit participants at the University of Minnesota from each of our SCI Medicine Fellowship clinical sites. We will also utilize local patient representative organizations by sharing posters and sample text for social media recruitment. The Rocky Mountain Regional Spinal Injury System at Craig Hospital provides comprehensive inpatient rehabilitation to over 200 newly injured individuals with SCI every year and continues to treat nearly 1,100 individuals with SCI annually in outpatient programs,

including Dr. Falci's neuropathic pain clinic. Similarly, the University of Minneapolis SCI system of care treats over 200 newly injured individuals with SCI every 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.

23.3 Study-Wide Recruitment Materials:
We will use flyers to recruit participants.

23.4 Communication Among Sites:
The site PIs (Falci, Morse) will communicate in person daily with their local teams to discuss experimental design, data analysis, and all administrative responsibilities. The research team (all key personnel across the 2 sites) will meet virtually on a weekly basis to monitor project progress and to trouble-shoot.

23.5 Communication to Sites:
Communication to sites will occur between the site PIs and study coordinators.

24.0 Coordinating Center Research

24.1 Role:
Dr. Morse will serve as PI for this proposal. As such, she will oversee implementation of all aspects of this proposal. Dr. Battaglino (UMN) will serve as co-investigator and will oversee the miRNA studies. Dr. Morse will oversee UMN recruitment, study coordination, data management, regulatory compliance, and dissemination activities. The UMN will serve as the statistical/data center for the study.

24.2 Responsibilities:
Each PI will share research results with other co-investigators, key personnel, and consultants. Publication authorship will be based on the relative scientific contributions of the personnel. Each PI will be responsible for their own fiscal and research administration.

24.3 Oversight:
Dr. Stillman will be the external medical monitor. As PI, Dr. Morse will oversee the study.

24.4 Collection and Management of Data:
A REDCap database will be created.

25.0 Resources Available

Resources Available: The PI is eligible to serve as PI, has sufficient time to serve as PI, and will contribute 4% effort in both years to this project. As such, she will oversee all aspects of this study.

26.0 References

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