Virtual Reality (VR) to improve Quality of Life in Patients diagnosed with Neurological Disorders

Principal Investigator:	*Leigh Charvet* *Neurology* *240 E 38th Street New York, NY 10016* *leigh.charvet@nyumc.org* *(929) 455-5141*
Additional Investigators:	*N/A*
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Study Product:	*HTC Vive Virtual Reality Headset*
Study Product Provider:	*HTC*
ClinicalTrials.gov Number	*NCT03606668*

Protocol version: 1/14/2020

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

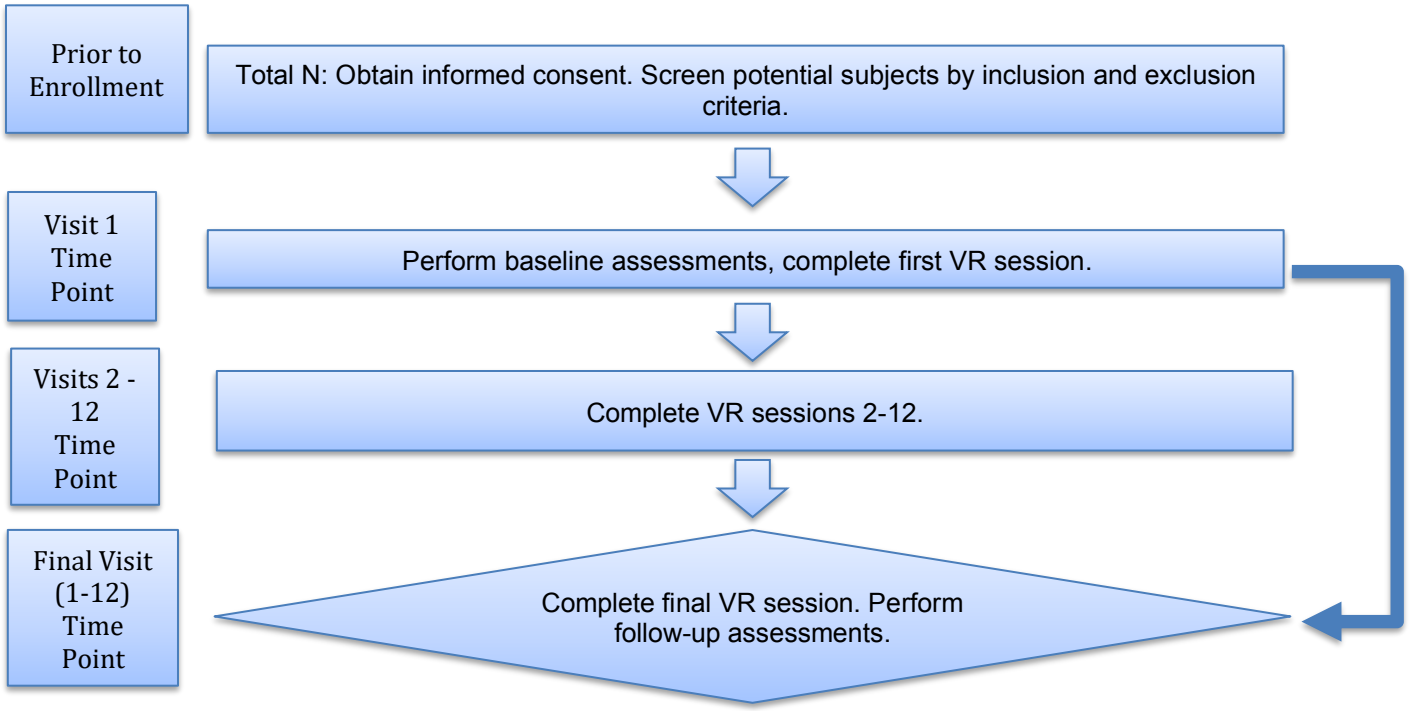
AE	Adverse Event/Adverse Experience
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
PI	Principal Investigator
VR	Virtual Reality
PwMS	People with Multiple Sclerosis

Protocol Summary

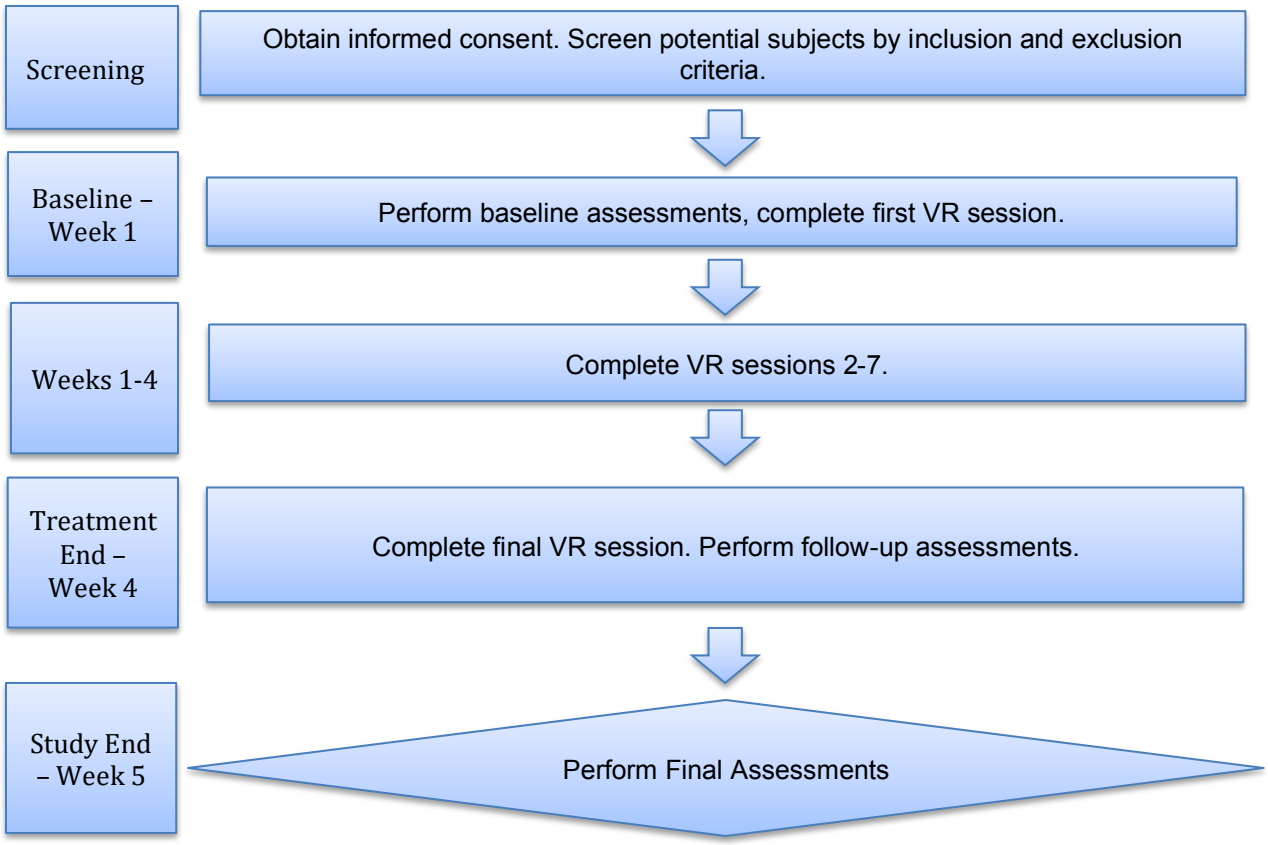
Title	Virtual Reality (VR) to improve Quality of Life in Patients diagnosed with Neurological Disorders
Short Title	*VR to improve Quality of Life*
Brief Summary	*Participants with neurological disorders will be recruited to complete sessions of virtual reality (VR) immersion. VR has been shown to have therapeutic benefit in certain patient populations and requires further clinical study to determine the extent to which VR can be used to rehabilitate and reduce symptom burden. This study seeks to pilot newly developed VR methods and collect preliminary data in order to support research grants and inform larger clinical trials. This proposed study will explore the tolerability and preliminary efficacy of Virtual Reality (VR), specifically to determine whether VR can acutely reduce the severity of symptom burden caused by neurological disorders.* *Additionally, a second group of MS participants with clinically significant pain will be recruited to test the analgesic effects of VR.*
Phase	*N/A*
Objectives	**Specific Aim 1: To test the feasibility and tolerability of immersive VR therapy in patients with neurological disorders.** **Specific Aim 2: To measure the efficacy of a VR program to manage chronic pain for people with multiple sclerosis.**
Methodology	*Study Group 1: Open-Label* *Study Group 2: Single blinded, randomized treatment allocation to one of two VR treatment conditions*
Endpoint	*Completion of up to twelve one-hour sessions of VR alongside study measures taken at the end of the last completed session*
Study Duration	*Participants may complete sessions for up to one year following consent.*
Participant Duration	*Study group 1: Approximately 12 hours over 12 days.* *Study group 2: Approximately 10 hours over 9 days.*
Duration of IP administration	*Up to 12 1-hour sessions, totaling twelve hours.*
Population	*Study group 1: Patients at least 12 years of age with a confirmed diagnosis of a neurological disorder* *Study group 2: Patients between the ages of 18 and 79 with a confirmed MS diagnosis and symptoms of MS pain.*
Study Sites	*NYU Ambulatory Care Center*
Number of participants	*104*
Description of Study Agent/Procedure	*HTC Vive VR Headset with interactive and/or relaxing games/video. The VR system and accompanying content will be configured by study personnel for comfort and therapeutic benefit.*
Reference Therapy	*N/A*
Key Procedures	*N/A*
Statistical Analysis	*Analysis will focus on change in quality of life measures from baseline to follow-up as well as the number of successfully completed VR sessions.*

Schematic of Study Design

Study Group 1 (Neurological Disorders):



Study Group 2 (Chronic Pain in MS):



1 Key Roles

Principal Investigator:
Leigh Charvet, PhD, Director of Research
New York University Langone Health - Multiple Sclerosis Comprehensive Care Center
222 East 41st Street, NY, 10016
929-455-5141
Leigh.Charvet@nyulangone.org

Co-Investigator:
Lauren Krupp, M.D.
New York University Langone Health - Multiple Sclerosis Comprehensive Care Center
222 East 41st Street, NY, 10016
929-455-5121
Lauren.Krupp@nyulangone.org

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

VR has become increasingly integrated into modern medicine, with both medical students and patients receiving education and receiving experimental rehabilitation therapies through the use of the VR medium [1]. Patients with neurological disorders stand to benefit from VR therapies [2, 3], as these diseases are often chronic and limited in treatment options.

In a series of preliminary studies, Hoffman et al (2004) investigated VR and subjective pain ratings with use of painful thermal stimuli and fMRI to monitor pain-related neural activity. VR reduced pain-related activity in all five regions of focus (Anterior Cingulate Cortex, Primary and Secondary Somatosensory Cortex, Insula, and Thalamus)[4]. In addition, VR reduced subjective pain-related reports as well as reduction in brain activity, displaying subjective and objective correlation of emotional and sensory aspects of pain experience [4]. In a separate study by Hoffman et al (2001), burn victims reported a lower subjective pain rating when experiencing VR while undergoing wound care than those who did not experience distraction. It was found that the magnitude of pain reduction did not diminish with repeated use[5]. The study results imply that VR use may have potential for implementation in other populations that experience neuropathic pain.

VR immersion therapy presents itself as a noninvasive, riskless, rehabilitative treatment with an abundance of promise for patients with unmet treatment needs [6]. VR immersion has been utilized for exposure therapy in posttraumatic stress disorders (PTSD) in Vietnam veterans as described in a case study by Rothbaum et al (1999)[7]. The patient was immersed in virtual environments in order to target memories triggered by each scene while being spoken to by the therapist through VR headset. Results indicated habituation and showed improvements on all measures of PTSD. PTSD scores using IES assessment lowered significantly following treatment end with sustained benefit for up to 6 months. Additionally, VR did not seem to create an adverse effect on conditions of depression, anxiety, or drug/alcohol use [7].

VR therapy using emotion-processing theory has been used to target anxiety disorders and fear arousal. Exposure therapy is a common treatment used to combat anxiety disorders such as specific phobias. Therapists attempt to desensitize the patient by associating relaxation techniques while presenting the feared object or situation [8]. VR allows for a passageway into exposure therapy whilst avoiding the actual fearful stimuli to the patient. Moreover, a study by Navarro-Haro et al. showed that participants who used VR in a mindfulness setting experienced subjective symptom relief in negative emotional states as well as reduced anxiety, sadness, and anger [9].

2.2 Rationale

Neurological diseases can confer varying symptoms in patients' lives that may cause physical, emotional, or psychological deficits. Common impairments include chronic pain, fatigue, depressed mood, and fine or gross motor issues, all of which have the potential to drastically affect a person's quality of life. Pain in neurological conditions is rarely disease-specific and patients can experience different types of pain within the same disorder[10]. Researchers and clinicians have begun to look to VR-based treatment modalities to reduce the severity of symptoms experienced such as neuropathic pain [3, 11], psychological distress[7, 12], and self-efficacy [13, 14].

We propose that immersive VR may be an effective means of reducing patients' symptoms through engagement of novel and immersive stimuli [15]. Such immersion is made possible through the use of groundbreaking computer graphics, surround-sound audio, and display screen headsets with high resolutions and body-tracking devices that allow video interaction with users in real-time [8].

2.3 Rationale for PwMS and Chronic Pain

Pain is the most common symptom associated with MS, affecting as many as 80% of all patients. As in other conditions, pain in MS is typically managed using medications including opioids and other centrally active drugs (e.g, antiepileptic medications such as gabapentin). However, pain medications are often not completely effective and can lead to dependence[16]. Pain medication can have many troubling side effects that can exacerbate other MS symptoms including fatigue and cognition. Therefore, there remains a significant unmet need for effective and tolerable pain management options [17, 18].

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Per HTC Vive manufacturer's specifications, study technicians will ensure the area around the patient is safe and with no obstructions. Immersive VR will be used under the supervision of the research assistant in charge of the session. Immersive VR may cause dizziness, nausea, or headache. **However, such adverse events are highly infrequent and we expect that the proposed treatment to be highly tolerated. This study poses minimal risk to participants**.
If discomfort is great enough that the participant wants to cease the session, the experiment will stop and symptoms should resolve after a brief rest.
This study poses no greater risk for children.

2.4.2 Known Potential Benefits

Participants may experience benefit from this study such as improvement in their mood or physical sensations. Immersive VR therapy may reduce symptom severity experienced by those with neurological disorders.

3 Objectives and Purpose

<u>Specific Aim 1:</u> To test the feasibility and tolerability of immersive VR therapy in patients with neurological disorders.
The primary outcome will be the number of successfully completed VR sessions across all participants. Secondary outcomes will be the subjective assessment of tolerability and engagement. Participants will rate enjoyment, engagement, and any potential side effects of the VR therapy.
<u>Specific Aim 2:</u> To test the effects of immersive VR on symptom burden in patients with neurological disorders.
The primary outcome will be the change in dimensions of symptom burden in participants with neurological disorders. Universal symptom inventory measures (Patient Reported Outcomes Measurement Information System or PROMIS) will be administered before and after each session. A paired t-test will be used to determine whether the cohort has experienced statistically significant change following VR.
The secondary outcomes will include disease specific inventories (i.e. MFIS) which will be administered before and after each session and their change after VR will be evaluated.

4 Study Design and Endpoints

4.1 Description of Study Design

Study Group 1 (Neurological Disorders):
The study is intended as a pilot trial for VR in neurological conditions. An open-label design will be implemented. Once participants are found eligible, they will complete one full session of VR using a headset preconfigured by study personnel. Participants will complete up to twelve sessions of VR therapy that may extend as long as an hour in length. Total number of study visits will be up to the study personnel's discretion. Study personnel will guide VR headset placement and program assignment (i.e., interactive or passive catalogues).

Study Group 2 (Chronic Pain in MS): The study will include an arm for people with MS (PwMS) and chronic pain. We will determine the efficacy of VR for the management of chronic pain in PwMS. Participants in this study group will receive eight treatment sessions over four weeks. Participants will be blinded to the VR treatment catalogue they receive.

4.2 Study Endpoints

4.2.1 Study Group 1 (Neurological Disorders): Study Endpoints

Primary study endpoint will be completion of at least one VR session and change in baseline measures.

Secondary study endpoint will be lack of tolerance of VR protocols. If a participant is unable to complete two full VR sessions due to any possible side effect (i.e. Dizziness or nausea) the session and participant's participation in the study will be terminated (see Assessment of Safety below).

4.2.2 Study Group 2 (Chronic Pain in MS): Study Endpoints

Primary study endpoint will be change in the Patient Reported Outcomes Measurement Information System (PROMIS) pain intensity and interference measures administered at baseline, treatment end, and study end.

Secondary outcomes will include additional measures of pain and other symptoms (i.e. mood and fatigue). We will also measure the acute effects of the treatment on pain before and after each VR session.

5 Study Enrollment and Withdrawal

5.1 Eligibility Criteria for Neurological Disorders

We will include participants who have a confirmed diagnosis of a neurological disorder. Exclusion criteria will include any health condition contraindicated with the use of a VR device (including uncontrolled epilepsy, vertigo, inability to balance, subpar visual and motor skills). See table 1 for full eligibility criteria.

Table 1: Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• At least 12 years of age • Has been diagnosed by a clinician as having a neurological disorder • Able to commit to the designated period of testing • Able to understand the informed consent process and provide consent to participate in the study • Capacity to complete study procedures as determined by screening personnel • SDMT Z-Score > -3.0 • WRAT4 Standard Score > or = 85	• Visual, auditory, and motor deficits that would prevent full ability to understand study • Visual, auditory, and motor deficits that would prevent full ability to operate VR equipment • Uncontrolled epilepsy • Current diagnosis of vertigo • Uncontrolled mood disorders • History of Psychosis or Schizophrenia

5.2 Eligibility for MS patients with Chronic Pain

We will include participants who experience pain as a symptom of their MS. Exclusion criteria will include any health condition contraindicated with the use of a VR device (including uncontrolled epilepsy, vertigo, inability to balance, subpar visual and motor skills). See table 2 for full eligibility criteria

Table 2: Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• **18-79 years of age** • Has been diagnosed by a clinician as having MS • Able to commit to the designated period of testing • Able to understand the informed consent process and provide consent to participate in the study • Capacity to complete study procedures as determined by screening personnel • **A Brief Pain Inventory interference score of at least 3 or more.** • **SDMT Z-Score > -3.0** • **WRAT4 Standard Score > or = 85**	• Visual, auditory, and motor deficits that would prevent full ability to understand study • Visual, auditory, and motor deficits that would prevent full ability to operate VR equipment • Uncontrolled epilepsy • Current diagnosis of vertigo • Uncontrolled mood disorders • History of Psychosis or Schizophrenia • **EDSS Score greater than 6.5** • **Unable to tolerate or manipulate VR treatment procedures (as evidenced by VR capability assessment)**

5.3 Vulnerable Subjects

Some participants referred may have cognitive impairment or other debilitating symptoms and could be considered a vulnerable population; however, those who lack capacity to consent will not be enrolled in this study. The capacity to consent will be assessed by the study personnel. Since it is not feasible to have an independent party assess every participant that intends to enroll in this especially low risk study, judgement of capacity to consent will be assessed by study staff. The symbol digit modalities test (SDMT) will be used to assess the cognitive status of participants and those who score three standard deviations below their age normative mean (indicating significant cognitive impairment) will be excluded from study. The SDMT can be easily administered in 90 seconds by trained study staff. It will be clearly explained and written for all potential participants that the study is entirely optional and there will be no negative consequences to their decision to not participate.

All child participants will complete a separate assent process in addition to their parent consent. It will be clearly explained and written for all potential participants that the study is entirely optional and there will be no negative consequences to their decision not to participate.

Pregnant women can be enrolled in this study and this study meets the definitions required by the applicable section of 45 CFR Part 46 Subpart B. Specifically, studies have been successfully conducting on nonpregnant women with no additional risk for pregnant women, the risk to the fetus is not greater than minimal and potential new applications to aid pregnant women may be developed through this research, pregnant women who would prefer not to stand, they will have the choice of completing the research protocol seated, and this research does not hold the prospect of direct benefit solely to the fetus and thus the father's consent is not necessary. No inducements, monetary or otherwise, will be offered to terminate the pregnancy. Study staff will have no part in any decisions regarding the timing, method, or procedures used to terminate a pregnancy. This research will play no part in determining the viability of the neonate. Children that are pregnant will not be included in this research.

Neither cognitively impaired people nor prisoners will be enrolled in this study.

5.4 Strategies for Recruitment and Retention

Method of Subject Identification and Recruitment
NYU Langone Medical Center has an extensive recruitment base. Patients who are seen by medical staff at the NYU Langone Medical Center, who fit the eligibility criteria, will be referred for the study by the study PI, Co-I, and sub-investigators. If the patient is interested and agrees, then a member of the study staff will contact them. Once the patient is identified, study staff will meet with the patient or call them to provide additional information regarding study participation. After the patient has reviewed the consent form and asked all the questions, and provides consent to participate, the patient will be enrolled in the study.

Study Group Recruitment
Both Participants with neurological disorders and participants with MS and chronic pain will be recruited for participation in this study in two separate groups: 1) individuals with neurological disorders, 2) PwMS with Chronic Pain.
To clarify, participants with MS and chronic pain will be specifically recruited for study group 2 to evaluate any analgesic treatment effects. Participants with MS without chronic pain may still be eligible for study group 1, which has broader recruitment criteria and primarily aims to demonstrate feasibility of treatment across neurological disorders.

Advertisements
An IRB approved flyer will be posted in local physician offices and waiting rooms throughout NYU, the surrounding community. A description of the study will be posted on sites related to neurological disorder.

A flyer will be created for each study group to recruit for both participant pools.

Ripple
Participant personal information may be kept in Ripple™, a secure web application designed for the storing and management of personally identifying information of research participants. Ripple was initially developed at the University of Michigan to provide a user-friendly, web-based secure interface where research teams can centralize the storage and management of research participants' personal information, including name, participant ID, demographics, and study workflow (e.g., appointments). Participant information managed with ripple is private and secure. This information is kept in fully encrypted format inside dedicated databases that are segregated from other Ripple accounts and thus only authorized study staff will have access to the study data. Likewise, Ripple infrastructure complies with the privacy and security guidelines of the Health Insurance Portability and Accountability Act (HIPAA), including 2048-bit data encryption in transit and at rest, automatic logoff, audit trail, daily backups in triplicate dedicated servers, firewall, custom access permission for lab members, zxcvbn password strength estimation, and enterprise administrative safeguards to prevent unauthorized staff from accessing participant information. Furthermore, Ripple is used only for storing personally identifiable information of participants and is not used to capture other research data (e.g., questionnaires, health records, etc.). This ensures that the personally identifiable information and research data are segregated. Ripple is already being used at NYU Langone Health.

5.5 Duration of Study Participation

The study will be open for enrollment for three years from the date of enrollment commencement.

Participants may complete as many as twelve study visits over the course of the study and these visits may be completed within one year of consenting. The amount of study visits that a participant will be asked to complete will be at the study personnel's discretion. If the first VR session is determined to be the final session for that participant, all baseline study measures will be re-administered immediately following the VR session.

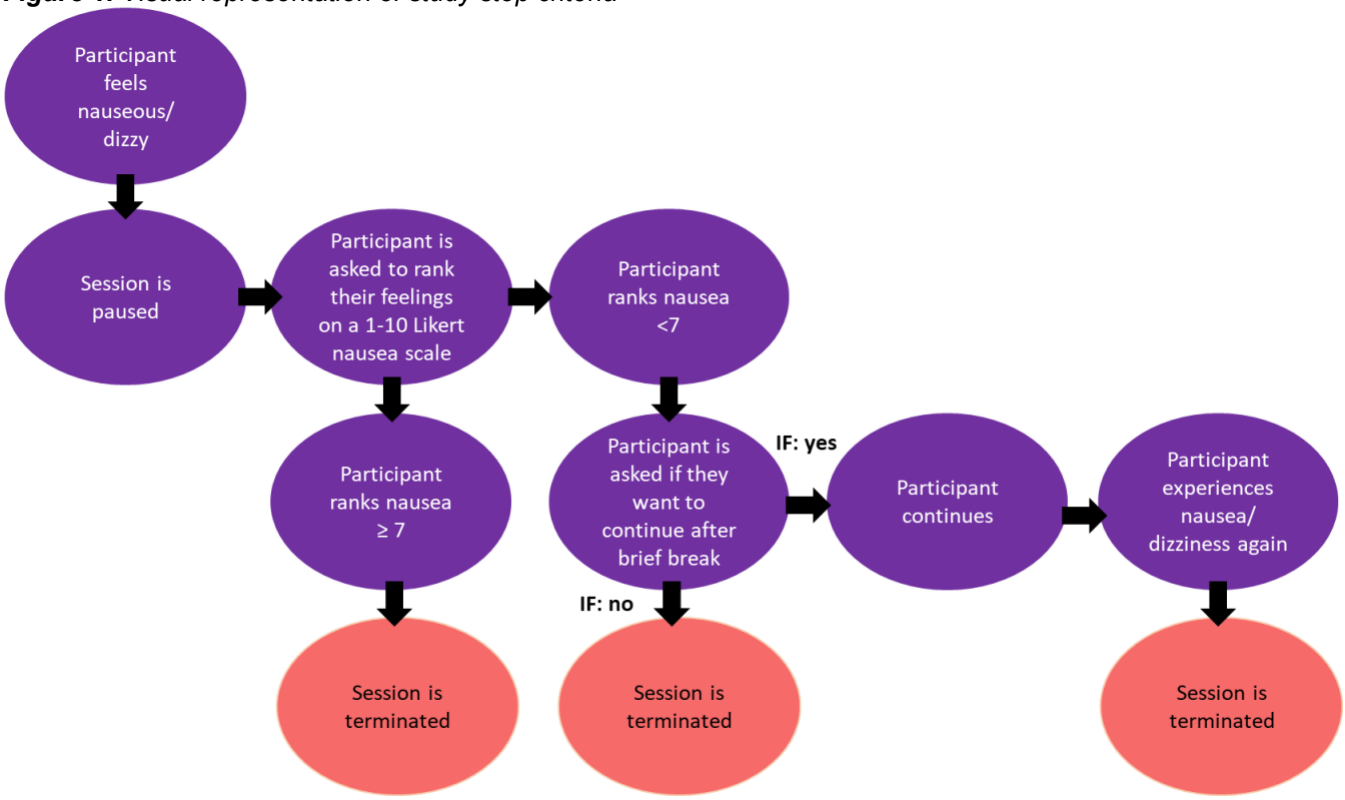
5.6 Total Number of Participants and Sites

Study Group 1 (Neurological Disorders): We will enroll a total of n=60 participants at a single site (NYU Ambulatory Care Center).
Study Group 2 (Chronic Pain in MS): We will enroll a total of n=44 PwMS and chronic pain at a single site (NYU Ambulatory Care Center)

5.7 Participant Withdrawal or Termination

Participants may withdraw from the study at any point for any reason.
Should a participant feel any adverse event such as nausea at any point during the VR sessions, the headset will be removed and the session will be paused. The participant will be asked to rate their adverse event, nausea for this example, on a 1-10 likert scale, 1 being mild and 10 being the need to vomit. If the participant rates their nausea at a level of 7 or more or expresses the need to vomit the session will be ended for that day. If the participant rates the nausea below a 7 and expresses the desire to continue, then the study personnel will wait with the participant (for up to 5 minutes) until the nausea is resolved and will then resume the VR session. Should the participant experience nausea a second time in the same session then the headset will be removed and that day's VR session will be ended (see Figure 1).
The participant's participation in the study will be terminated if two VR sessions are cancelled due to nausea or if participants express the desire to stop.

Figure 1. *Visual representation of study stop criteria*



6 Study Device

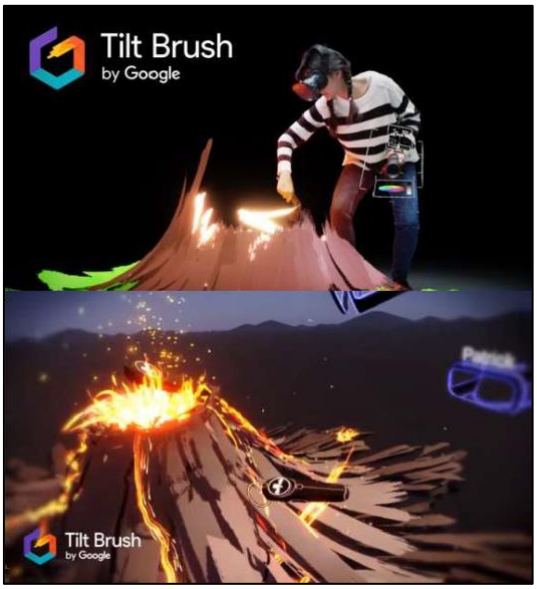
6.1 Study Device Description

We will use the HTC Vive VR system running on a high performance desktop computer.

6.1.1 Administration of Device

Participants will be able to complete a maximum of twelve 1-hour sessions of virtual reality featuring two separate treatment catalogues of interactive experiences, games, or videos.

Figure 2: Painting on a Virtual Canvas



A) The interactive catalogue includes a virtual 3D canvas that participants may paint upon, completion of daily tasks in a virtual kitchen, guided virtual meditation, interaction with music corresponding to the beats per minute of a song, virtual assessment of hand-eye coordination and range of motion among other experiences. See Figure 2 for an illustration of the virtual painting program.

B) The passive VR catalogue includes videos that are non-interactive and passively viewed. Participants may look in 360° at videos that include nature (i.e. underwater biomes, penguins and other animals, earthly biomes), education, and art among others in relaxing or exciting environments.

Participants may receive one of these two catalogues to complete over the course of their participation, regardless of study group assignment.
Each session will be supervised by a study technician trained to troubleshoot any problems related to the VR system, computer, games, or participants' intolerance of VR. All sessions will be completed at the NYU Ambulatory Care Center.

6.1.2 Procedures for Training of Clinicians on Device

Formal training for study technicians will focus on familiarity with the computer and VR system and ensuring participant safety.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

Participants will complete an informed consent form before any study procedures begin. Participants under the age of 18 will complete an assent form while their legal parent or guardian will complete a consent form.
Participants will complete relevant assessments listed in Table 2 before undergoing a VR session.
Participants may complete as much as one hour of VR therapy during any given session.

Study Group 1: There may be as many as twelve VR sessions during the course of the study. Study personnel will be available to guide participants during the entire duration of the VR session and ensure each session is completed safely. VR treatment will entail use of computer software designed to immerse participants and engage them in exercises. Software includes virtual painting, walking through vivid and calming settings, solving puzzles, among others.

Study Group 2: Similar to study group 1, study personnel will be available to guide participants throughout each VR session. VR treatment will be identical to study group 1.
Participants with MS will only be able to receive eight treatment sessions in this study group and will complete their treatment over four weeks.
Two treatments sessions must be completed each week (of the four weeks) and separated by at least one day. For example, if a participant completes one of their weekly treatments on Monday, they are not able to complete the treatment on Tuesday but may come in on any of the remaining weekdays that study staff are available.
Participants will attend a baseline visit with assessment and training procedures and receive their first treatment immediately after all baseline assessments. Participants will then complete the remaining seven treatment sessions over four weeks. At the final treatment session, participants will repeat assessments. One week following the final treatment session, participants will be asked to return to clinic to complete assessments once more to test cumulative benefits one week following treatment end.

7.2 Study Outcome Measures

Table 3 below lists all outcome measures and time points at which they will be completed.

Measure	Screening***	Baseline/First Session	Follow-up/Treatment Sessions	Final Visit
Symbol Digits Modalities Test (SDMT)	X	X	X**	X
Wide Range Achievement Test (WRAT-4)	X			
VR Tolerability and Competence Test	X	X		
VR Session Questionnaire		X	X	
Pre and Post VR Session Evaluation		X	X	
Baseline VR Experience Questionnaire		X		
Study End VR Experience Questionnaire				X
Neuro-Quality of Life Questionnaires*		X	X	X
PROMIS Measure of Fatigue, Mood and Health Related Quality of Life**		X	X	X
Fatigue Severity Scale*		X	X	X
Beck Depression Inventory*		X	X	X
Positive and Negative Affect Schedule**		X	X	X
Rey Auditory Verbal Learning Test*		X	X	X
Brief Visuospatial Memory Test - Revised*		X	X	X
King Devick Test*		X	X	X
Cogstate Brief Battery*		X	X	X
Grooved Pegboard*		X	X	X
Grip Strength*		X	X	X
Test of Everyday Cognitive Abilities*		X	X	X
Modified Fatigue Impact Scale*		X	X	X
Cognition Lab*		X	X	X
Pain Catastrophizing Scale**		X	X	X
Symptom Catastrophizing Scale**		X	X	X
Immersion Rating Scale*		X	X	X
Toronto Mindfulness Scale**		X	X	X
Spatial Positioning Recording*		X	X	X
Brief Pain Inventory**	X	X	X	X
Automatic Thoughts Questionnaire – 30 Item**		X	X	X
Wong-Baker Faces Pain Rating Scale**		X	X	X

*:Optional measures that may be excluded based on study personnel judgement.
**: Optional for study group 1 but required for study group 2 (Chronic Pain in MS).
*** Screening assessments may be used as the Baseline assessment if Screening and Baseline are within two weeks.

8 Assessment of Safety

Per HTC Vive manufacturer's specifications, in-clinic participation will ensure the area around the patient is safe and with no obstructions. Immersive VR will be used under the supervision of the research assistant in charge of the session. Immersive VR may cause dizziness, nausea, or headache. **However, such adverse events are highly infrequent and we expect that the proposed treatment to be highly tolerated. This study poses minimal risk to participants**.

If discomfort is great enough that the participant wants to cease the session, the experiment will stop and symptoms should resolve after a brief rest. Additionally, this study poses no greater risk for children.

We will utilize operating procedures for reviewing patient safety data and source data generated from this study. If after the first 10 subjects the compliance or incidence of adverse events is poor, the study will be put on hold and reviewed. Safety is emphasized in our study protocol and risk is minimal in that there should be no harmful, long term side effects or adverse effects from the VR sessions.

An adverse event is defined as any experience that negatively affects the wellness of a participant that can reasonably be attributed to the effects of the VR treatment. Adverse events that are unexpected, harmful, and related to the VR will be reported to the IRB. Examples of adverse events that are expected include: dizziness, nausea, vertigo, headache, etc. The PI will evaluate and follow AEs and AEs that are not severe as determined by the PI will be submitted within 5 business days of the occurrence of the event.

Specific attention will be given to data quality and timeliness, HIPAA-compliant, safe storage of data, and data backup of electronic source data. Attention will also be given to participant recruitment, participant risk versus benefit, adverse events, and other factors that can affect study outcome, including scientific or therapeutic developments that may have an impact on the safety of the ethics of the study.

We will submit data safety monitoring reports to the IRB after 10 participants are enrolled, and follow with reports for each further increment of 10 active enrollees. The study PI will review data safety reports in order to assess whether AE incidence rate is on par with that in publisher literature[19]. The research coordinator will submit data safety monitoring reports reviewed and signed by the PI. Any adverse effects, such as feelings of nausea, will be catalogued and quantified to determine rates of incidence. If the rates of incidence are higher than previously expected by PI based on literature then the study will be placed on hold and assessed. The most common adverse event expected is motion sickness and nausea, of which estimates of incidence vary across studies as technology has advanced and varied greatly over the last 20 years (some studies report 97% of participants as reporting none to mild nausea[19]). We conservatively expect a 20% incidence rate for feelings of motion sickness or nausea. We also expect other adverse event incidence rates such as headache, vertigo, and seizures to be exceptionally low, below 5% of occurrence.

9 Statistical Considerations

Study Group 1: As this is an exploratory protocol that is collecting data for future power analyses, the designation of recruiting 60 human subjects is somewhat arbitrary. Following the results and any benefit experienced by these initial participants, future clinical trials can be conducted with properly powered samples. Recruitment of 60 participants would allow for enough data for a sufficient power calculation for future trials to determine clinical efficacy.

Preliminary paired sample t-tests will be conducted to determine whether participants experienced statistically significant change in neurological disorder symptoms.

General means and standard deviations will be reported and analyses will inform future power analyses of clinical trials that will use VR as a treatment modality.

Study Group 2: The second pool of participants will be n=44, following preliminary effect size analyses. Participants who complete at least 6 of the 8 (75%) total sessions will be included in analyses, and we have anticipated a dropout rate of up to 10%, resulting in 20 or more completers in each group.

Primary outcome will be the change in PROMIS Pain interference from baseline to the study end visit. Based on a previous, successful clinical trial in chronic pain also using an 8-session nonpharmacologic intervention[20], we can expect to have 89% power to detect a significant group difference between the two study conditions. We will also compare change between the groups from baseline to treatment end on the additional self-report measures.

Secondary outcomes will be change in pain visual analog scales completed before and after each session to evaluate acute treatment effects and changes in medication usage from baseline to treatment end measured qualitatively[21]. We will also analyze pain before and after each VR session with the Wong-Baker Faces Pain Rating Scale to compare the immediate analgesic effects of each condition and this cumulative change across sessions.

10 Source Documents and Access to Source Data/Documents

Data will be entered in the HIPAA-compliant NYU REDCap database designed specifically for this study. An anonymous database number will be assigned to each participant and will be used for both the Data Entry Sheet and the Patient Follow-up Sheets. The original consent, which includes the patient name and ID number, will be stored separately in a locked filing cabinet in a locked office. Access to this data will be restricted to study personnel only. Research data will be entered online through the secure NYU database software REDCap and source documents will be kept in a locked filing cabinet in a locked office. Participant data will be coded by the assigned ID and identifying information will not be presented or published to maintain participant privacy and confidentiality.

11 Quality Assurance and Quality Control

- Development of standard protocols to perform all data collection and follow-up activities.
- Use of standardized forms.
- Uniform criteria for patient recruitment.
- Standardized data processing.
- Regular communications between study staff and study investigators to resolve questions.
- Performance monitoring of data collection and data processing activities, as well as preparation of periodic reports and analyses on performance monitoring.
- Monthly monitoring of recruitment statistics.

12 Ethics/Protection of Human Subjects

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Informed Consent Process

All potential participants will complete a screening interview to ensure general eligibility. The study staff member speaking to the subject will provide the subject with an overview of the study and verbally receive their permission, under a waiver of documentation of consent, to complete the general eligibility screening. The pre-

screening measures will inquire into demographic background, any auditory, visual, or motor impairment, disclosure of neurological disorder, and current medication use. This phone screen is minimal risk to the participant and collected information will be maintained in secured, locked files. De-identified information (assigned a study screening code) will be entered into a secure, NYU approved online screening database. If a participant is not eligible, they will be considered a screen fail. No additional information will be collected. PHI will be destroyed immediately if a participant is not eligible or does not return to sign written consent/authorization to participate. Only study staff will have access to these records. Once the participant is generally eligible, the PI, or one of the trained study team members will review the consent form with the subject and explain the purpose of the study, the procedures, as well as risks and benefits. All questions will be addressed before acquiring the participant's signed consent. Subjects must have capacity to consent in order to be enrolled in the study. Referring clinicians and NYU clinicians doing the medical screening will be responsible for assessing the capacity to consent. An independent assessor will not be utilized.

12.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol

- *Study Consent (Adult and Pediatrics)*
- *Study Assents (12-14 and 15-17)*

12.3.2 Consent Procedures and Documentation

Subjects who are eligible for this study and are over 18 years of age will be asked, following an appropriate discussion of risks and benefits, to give consent to the study for further study procedures. When a minor who was previously enrolled in the study through parental or a guardian's consent and participant assent turns 18 years of age, they will complete a new consent form for adults (they will not require parental or guardian signature as an adult) before the completion of any further study procedures.

Parental Permission**:** A portion of subjects who are eligible for this study are under 18 years of age, and written permission from parents or legal guardians will be required for participation. After determining that a subject is eligible, the site investigator or designee will approach the parent or legal guardian to offer participation for their child in the study. The parent or legal guardian will be informed about the objectives of the study and the potential risks and benefits of participation. If the parent or legal guardian refuses permission for their child to participate, then all clinical management will be provided by the clinical staff in accordance with institutional practice and judgment.

Child Assent**:** Children will be asked, following an age-appropriate discussion of risks and benefits, to give assent to the study or further study procedures.

Subject Capacity: All participants will be confirmed to have the capacity to provide consent by a member of the core physician group as described above. Any participants that could minimally meet the criteria for cognitive impairment will not be enrolled into the study.

Debriefing Procedures: No information will be purposely withheld from the subjects. A clinical neuropsychologist (PI) and the treatment ream will be available to answer any questions concerning the tests and results that may arise. An enrollment log will be maintained and consent and assent forms will be kept in secure location separate from the participant's data.

After review of the consent or assent form and prior to the start of the first session, the PI or one of the trained study staff members will obtain written consent or assent with a signature of the patient on the consent or assent form. All original signed consent forms will be maintained in the study file, separate from the participant data.

12.4 Participant and Data Confidentiality

Information about study subjects 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 subject authorization informing the subject of the following:

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

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects 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 subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

13 Data Handling and Record Keeping

13.1 Data Collection and Management Responsibilities

Paper and computerized data will be collected. Data will be entered in the HIPAA-compliant NYU REDCap database designed specifically for this study.

13.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 Protocol Deviations

All protocol deviations will be addressed in study source documents and reported to the IRB.

13.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post market surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

14 Study Finances

14.1 Costs to the Participant

If subjects choose to participate, the VR immersion sessions will be provided to them without cost. There is no cost to participants.

14.2 Participant Reimbursements or Payments

Subjects will be compensated $10 per session per patient for their participation in the study. The payment will be finalized and sent for processing once the participant has completed the extent of their study participation (i.e. if a participant completed 10 study sessions then after the 10^{th} session their form will be submitted for processing for $100).

15 Conflict of Interest Policy

The investigators and research team members have no conflict of interests in relation to this study.

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16 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Study Consent forms: Adults and pediatrics versions
- Study Assent forms: 12-14 and 15-17 versions
- Study Flyer
- Study measures listed in table 3.