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A Telehealth tDCS Approach to Decrease Cannabis Use: Towards Reducing Multiple Sclerosis Disability

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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
BDI	Beck Depression Inventory
BICAMS	Brief International Cognitive Assessment for MS
BVMT	Brief Visuospatial Memory Test
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
CUD	Cannabis Use Disorder
CUDIT-R	The Cannabis Use Disorder Identification Test – Revised
CWS	Cannabis Withdrawal Scale
DCC	Data Coordinating Center
DFAQ-CU	Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis-Use Inventory
DHHS	Department of Health and Human Services
DLPFC	Dorsolateral Prefrontal Cortex
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
K10	Kessler Psychological Distress Scale
mA	Milliamperes
MCQ-17	Marijuana Craving Questionnaire-17
MOP	Manual of Procedures
MS	Multiple Sclerosis
N	Number (typically refers to participants)
NIH	National Institutes of Health
NSR	Non-significant risk
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research

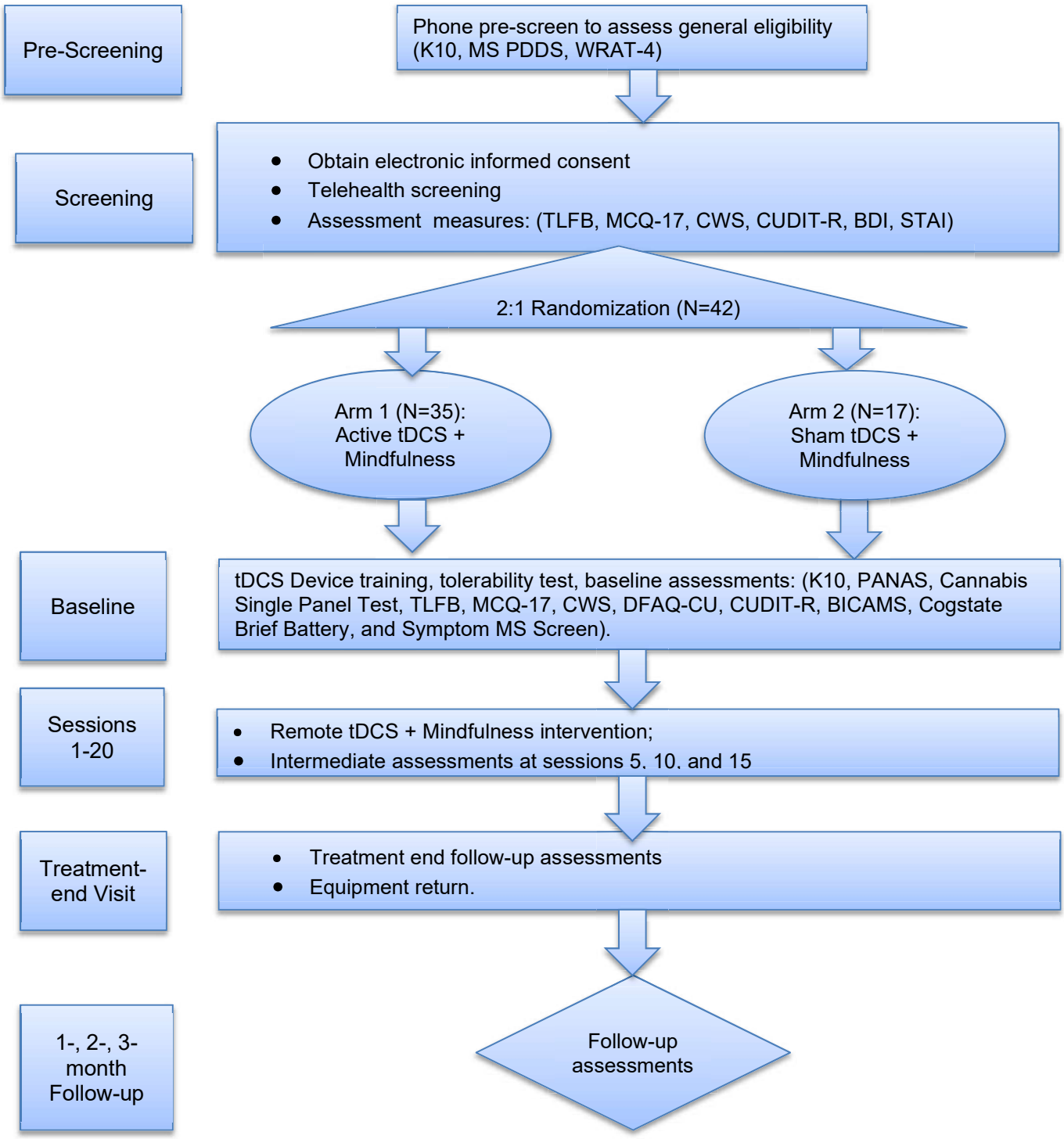
PANAS	Positive and Negative Affect Schedule
PDDS	Patient Determined Disability Scale
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RAVLT	Rey Auditory Visual Learning Test
RRMS	Relapse Remitting Multiple Sclerosis
SAE	Serious Adverse Event/Serious Adverse Experience
SDMT	Symbol Digit Modalities Test
SOP	Standard Operating Procedure
STAI	State-Trait Anxiety Inventory
tDCS	Transcranial Direct Current Stimulation
TLFB	Timeline Followback Method Assessment
US	United States
TMS	Transcranial magnetic stimulation

Protocol Summary

Title	A Telehealth tDCS Approach to Decrease Cannabis Use: Towards Reducing Multiple Sclerosis Disability
Short Title	A Telehealth tDCS Approach to Decrease Cannabis Use in MS
Brief Summary	We will recruit 52 patients with MS, CUD, and elevated distress (K10 score 10-35) in a double-blinded, parallel-arm, sham-controlled trial of a completely at-home intervention. We will test 20x20-minute RS-tDCS (2.0 mA, DLPFC: left anodal) paired with guided mindfulness meditation to decrease distress and cannabis use. Participants will be randomized 2:1 to active vs. sham tDCS.
Phase	Phase 2
Objectives	- Evaluate the effect of DLPFC tDCS to decrease distress component of cannabis use disorder - Evaluate the effect of DLPFC tDCS to reduce cannabis use - Evaluate if DLPFC tDCS related change in cannabis use is linked to a change in distress
Methodology	2:1 Randomized, Parallel-Arm, Double-Blind, Sham-Controlled Design
Endpoint	Primary Endpoints: - Decrease in Distress by treatment End - Decrease in Cannabis Use by treatment End Secondary Endpoints: -Decrease in Distress through 3-month follow-up -Decrease in Cannabis Use through 3-month follow-up
Study Duration	2 years
Participant Duration	Approximately 4.5 months (4-6 weeks of intervention + follow-ups at 1, 2, and 3 months)
Duration of IP administration	20x20 minutes daily sessions of DLPFC tDCS combined with mindfulness meditation
Population	N=52 female participants (ages 21-65) with RRMS and CUD
Study Sites	NYU Langone Health 222 East 41st Street, 10th Floor New York, NY 10017
Number of participants	N=52 participants expected to be enrolled at NYU Langone Health
Description of Study Procedure	tDCS is noninvasive brain stimulation device that modulate brain activity delivering a low-intensity electrical current (2.0 mA) through scalp sponge electrodes. Participants will follow an audio track for guided mindfulness during the stimulation. For Active tDCS, the device is programmed to ramp up to 2.0 mA (for 30 seconds), provide constant current throughout session (19 minutes), and then ramp down (for 30 seconds) at the end. For Sham tDCS the device is programmed to ramp up to 2.0 mA (for 30 seconds) followed by a ramp down (30 seconds), with no current delivery for 18 minutes, and then ramp up (for 30 seconds) and down (for 30 seconds) at the end.
Reference Therapy	

Key Procedures	Active or sham tDCS with simultaneous mindfulness meditation
Statistical Analysis	Multivariate linear regression will be used to evaluate the outcome of each Aim. The dependent measures will be nested within timepoint (Visit 1, 5, 10, 15, 20), with active/sham as fixed effects.

SCHEMATIC OF STUDY DESIGN



1 Key Roles

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Multiple sclerosis (MS) is a common neurological disorder, affecting over one million in the U.S. alone[1], many of whom are younger adults in the peak of their most productive years.
MS is a chronic and progressive CNS disease that is characterized by demyelination, immune-mediated inflammation, and neurodegeneration[2,3], and is without cure. It typically (85%) presents as relapsing-remitting, defined by acute episodes (e.g., motor and/or sensory dysfunction), followed by relative recovery and stability[4]. MS results in cumulative damage over time, with a broad and varying range of persisting symptoms[5,6]. The aggregate daily impact of MS symptoms and reduced quality of life defines its disease burden[7], which can result in devastating disability in otherwise healthy adults[8–10]. While MS disease-modifying therapies (DMTs) are valuable in slowing disease activity[11,12], they do not directly target its symptoms[13].

Cannabis Use Disorder (CUD) is a common problem for people living with MS.
Cannabis use (smoking/vaping/ingestion) has grown exponentially in the U.S.[14], further accelerated in the context of the COVID-19 pandemic[15–17]. While less likely than the general population to use alcohol or tobacco, more than one half of all patients with MS use cannabis[18]. The large majority of this use is outside of medical direction[18], typically either as recreational or self-directed management of nonspecific problems (e.g., mood, pain, sleep). While cannabis is thought to be benign or even health-promoting among some patients with MS, it is only prescribed in a minority (≈4%)[18,19] where available[20,21], with insufficient evidence to support any therapeutic use in MS other than for spasticity[22,23] (modest evidence for treating spasticity[24], insufficient for all other symptoms[25], including neuropathic pain[26]). As a result, many patients with MS have become frequent and habitual users[27] in the cycle of addiction[28].

Cannabis use worsens MS disease burden[29].
While cannabis can vary widely in its ratio of its key components tetrahydrocannabinol (THC) and cannabidiol (CBD), both can dampen brain activity[30,31] adversely influencing cognitive functioning[32,33] and mood[84,34], and their respective neurobiological substrates[35,36]. The problematic neuropsychiatric consequences are well known[37] and can be especially critical in the context of MS[29,38–42]. The high prevalence of cannabis use in MS is a challenge for prospective study, with investigators instead demonstrating the therapeutic gains following its discontinuation, including restoration of aspects of brain activity[43], reduced depression[44], and improved cognitive functioning[43]. The benefit to MS-related cognitive impairment is particularly urgent, given that it is among the most disabling disease features[45] and occurs in

>75% of all patients at any point in their disease course[46,47]. Initially characterized by slowed information processing[46], reduced cognitive functioning can be subtle but often disables otherwise neurologically intact patients, compromising the ability to meet both work and family responsibilities[48]. Cannabis use causes further impairment[37,49], a finding that is consistent across other chronic brain disorders[50,51].

We propose to target the distress that perpetuates the addiction cycle.
Psychological distress[52] is an emotional health status marked by negative affect (e.g., feeling anxious, agitated, tense, irritable). As described in Koob & Volkow's 3-stage model of addiction[53,54], negative emotional states[52,55] are key drivers of the addiction cycle. Distress is a result of disordered cannabis use, and in turn, also drives its continued use (i.e. "to cope"). Distress resulting from the disordered use of cannabis is well documented[56,57], and patients with MS are likely to be at even greater vulnerability to the distress component of addiction[58–62]. As the state of distress is often below the threshold of clinical depression or anxiety disorders, it remains an under-detected and undertreated aspect of the cannabis addiction cycle.

The dorsolateral prefrontal cortex (DLPFC) is a key neural circuit for negative affect[63–66].
With growing knowledge of the neural circuits that contribute to treatment of substance use disorder in general[63,67–69], there is an emerging interest in neural circuits as a target for intervention[70]. By targeting distress, we expect reduction in use of cannabis and corresponding improvements in subjective well-being[71].

Investigations are currently focused on evaluating the efficacy of a variety of noninvasive brain stimulation techniques for application in substance use disorders, using transcranial direct current stimulation (tDCS)[72] or transcranial magnetic stimulation[73] (TMS) as tools to modulate the DLPFC neural circuitry[69,70]. We propose here the use of tDCS, where direct electrical current is delivered to cortical tissue via scalp electrodes with the goal of raising the resting membrane potential of the neurons and resulting in the higher likelihood of firing[74]. In this manner, repeated applications of tDCS are used to modulate neuronal activity in regions of interest[75].

DLPFC tDCS has a strong body of evidence supporting its use for distress reduction.
Multiple RCTs have shown that repeated application (i.e., ≥20 daily sessions) of tDCS, targeting the DLPFC, reduces distress in other clinical disorders, such as in the context of depression[76] and anxiety[77] (and has received regulatory approval for clinical use in mood disorders in the EU, UK, Australia and Brazil[78]). Further, we are currently leading the U.S. FDA-commissioned study of tDCS for depression using the Remotely Supervised tDCS (RS-tDCS) platform as proposed here[79,80]. Our extensive experience with tDCS in patients with MS, and without depression, has shown that the DLPFC tDCS (vs. other targets such as primary motor cortex) reliably decreases negative affect. Importantly, these changes have also been linked to increased functional connectivity in the DLPFC following treatment[81].

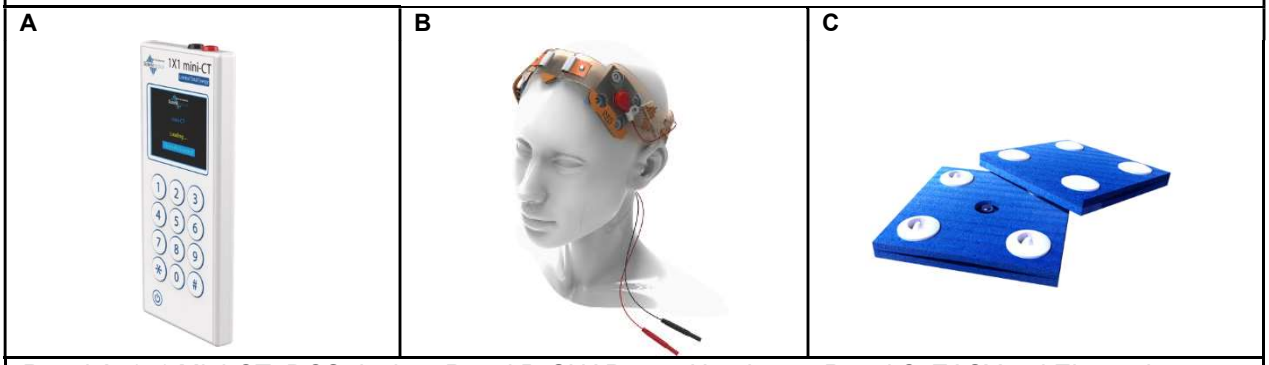
tDCS must be dosed in a sustained and cumulative manner for adequate evaluation of its efficacy.
It is clear that tDCS effects are cumulative with adequate evaluation of behavioral effects requiring a period of multiple repeated applications[82]. Preclinical studies have demonstrated that stimulation results in sustained neuronal response[75], with increased sensitization following repeated application[82]. This effect is mirrored through consistent findings across clinical studies in that: **1)** a single tDCS session doesn't cause any meaningful behavioral response, and **2)** behavioral changes only follow a sustained period of daily treatment[83,84].

2.2 Name and Description of the Investigational Device

- **1x1 Mini-CT tDCS device** *(Soterix Medical Inc.)*: The 1x1 Mini-CT tDCS device (see Fig.1, *Panel A*), through the accompanying headset (Fig. 1, *Panel B*) and sponge electrodes (Fig.1, *Panel C*), delivers a weak electrical current (1.0-2.0 mA) to target a specific area of the brain. It is a powered device (9 V) and is easily operated, with a user-friendly large-button keypad interface. The device has specific functions and features that guarantee safety in the remote supervised administration and uniform stimulation dose across sessions and participants. The device allows strict dose

control and usage control, employing a one-time use code provided by the study technician to unlock the device for each stimulation session.

Figure 1. Equipment for tDCS intervention



Panel A: 1x1 Mini-CT tDCS device; *Panel B:* SNAPstrap Headgear; *Panel C:* EASYpad Electrodes

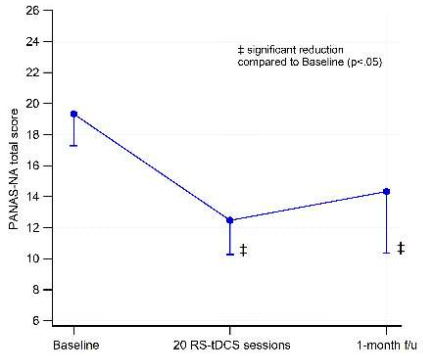
2.2.1 Preclinical Data

N/A

2.2.2 Clinical Data to Date

Feasibility of RS-tDCS. We have led the field in home-based brain stimulation with the development of the RS-tDCS platform[85–95]. In our protocol, participants are provided with remotely-controlled tDCS device, trained in safe and effective operation, and then supervised for daily use through live videoconference[96] (VSee[96]). Our updated videoconference will be Zoom or Webex. The telehealth connection has resulted in high retention rates across repeated and extended sessions (e.g., >97% completion rates across RCTs to date[85–95]). Extensively tested over > 7 years (>9000 at-home tDCS sessions in >400 patients to date), it is well validated for use in MS and generalizable for use across most other clinical populations[85–95] (ages 18-80 years, range of neurological and psychiatric conditions, including those with advanced disabilities and/or limited technical experience, and reaching those at socioeconomic disadvantage). Further, the RS-tDCS platform has allowed for continued enrollment of patients with MS in ongoing RCTs during the COVID-19 onsite clinical research pause[97–100] (with >100 participants by completing all study procedures from home).

Figure 2. 20 RS-tDCS DLPFC sessions significantly reduces negative affect in an MS sample



*Reduction in negative affect was maintained at 1-month post treatment f/u

DLPFC tDCS regulates negative affect. DLPFC tDCS has been established to reduce distress (e.g., in mood disorders[101,102] and other psychiatric conditions[103]). In subanalyses of nondepressed MS participants with high baseline negative affect[55] ,10 or more RS-tDCS sessions, led to reliable negative affect reduction (Fig. 2), and the negative affect reduction was maintained at 1-month follow-up. Importantly, these changes have also been linked to increased functional connectivity in the DLPFC following treatment[81].

2.2.3 Dose Rationale

The tDCS protocol of this proposed research will use a stimulation intensity of 2.0 mA that falls well within safety limits established by numerous previous studies applying tDCS with human subjects.

2.3 Rationale

The application of tDCS to substance use disorder is not novel on its own[70]. However, no study to date has evaluated tDCS for the treatment of CUD[104], and all studies of tDCS in other substance use disorders have required onsite delivery of treatment, resulting in mixed findings following "underdosed" treatment periods in terms of number of applications (i.e., <5) and duration of treatment period (i.e., 1 week or less)[105]. Further limiting comparison/conclusion across studies to date has been the broad variation in other parameters such as electrode montage, stimulation intensity, duration, frequency, and concurrent activity during the stimulation[70,104]. tDCS represents a promising treatment to reduce the distress component of the addiction cycle, and must be evaluated in a dosage that is likely to be effective.

Hypothesis: When given in a multisession paradigm, active vs. sham tDCS delivered to the DLPFC will reduce distress and cannabis use in patients with MS.

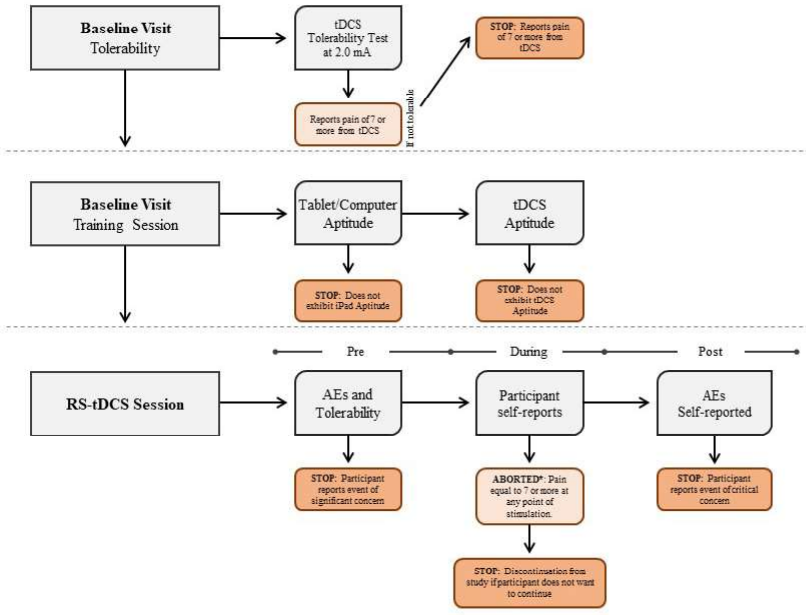
2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

- **Risks of tDCS:** The repeated application of tDCS as proposed in this study poses a non-significant risk (NSR) to participants. The safety of this technique has been addressed and tested by multiple researchers who have concluded that tDCS, as applied in a manner similar to our proposed protocol, induces only mild and transient side effects with no report of serious adverse event related to tDCS across clinical trials to date. In >9,000 participant, no undesirable or long-lasting effects have been reported, nor have any subjects reportedly abandoned a study due to discomfort. The most common side effects are warming sensation, itching or tingling sensation under the area of the electrodes. The tDCS protocol of this proposed research will use a stimulation intensity of 2.0 mA that falls well within safety limits established by numerous previous studies applying tDCS with human subjects. In both active and sham tDCS treatment arms, there could be mild discomfort from wearing the headgear.

  The protocol is designed to have a decision-tree series of checkpoints with "STOP" criteria that must be cleared in order to proceed at each step (see Fig.3).

Figure 3. Safety and Tolerability checkpoints and stop criteria



* the supervising study technician intervenes to assess the subject's safety and abort the session when necessary.

- **Guided mindfulness meditation**: Mindfulness meditation is not associated with any known risk. To minimize possible frustrating feeling, each session will be monitored in real-time via HIPAA-compliant videoconference with a trained study technician.

- **Self-report questionnaires**: Completing questionnaires about one's physical and mental health and cannabis use may produce some discomfort and/or emotional distress in some patients. Participants will be allowed to take breaks as needed and may skip questions they do not feel comfortable answering so long as the questions do not affect analysis of primary endpoints or eligibility criteria. While we don't anticipate this population to have suicidal ideation, Dr. Charlson MD will screen for suicidality as part of the research eligibility screening and will follow standard clinical procedures if a subject is suicidal (e.g. refer subject to closest emergency room).

- **Single panel urine test**: Completing the procedure for urine strip testing in the context of video visit may cause some emotional discomfort. Participants may become upset if the results of the strip test are not consistent with their self-reported use.

2.4.1.1 Other Risks

- **Breach of Confidentiality**: There is minimal risk of breach of confidentiality. Participants will be assigned a unique study ID and their name will not be used on any of the data collected. All study data survey will be acquired through REDCap and the printed records will be stored in lock cabinet at 222 E 41st Street, 10th Floor. Any study data stored on secure NYU computers and servers will be de-identified. The results of these data collected may be used for publication but will not include the participants' names. Drug test results will not be added to subjects' medical records and will not be stored with any PHI.

- **Unforeseeable Risks:** While not expected, there may be risks associated with tDCS that are not known at this time.

2.4.2 Known Potential Benefits

Some participants may receive benefit from the mindfulness meditation program. There is robust research on the mental health benefits of mindfulness meditation (e.g. reduced distress and anxiety).

Other potential benefits include a telehealth screening with a licensed clinician that could be of benefit to subjects if the results of these evaluations are utilized in their future health care.

This will be the first study to evaluate a tele-intervention program of tDCS for reducing distress and cannabis use in MS. The project has the potential to produce an immediately available treatment option for distress and CUD that could be generalized to other substance use disorders. This would have immediate and significant clinical utility. In particular, the benefit to the field is the availability of treatment option for managing symptom burden, generalizable to the common use of cannabis in other chronic brain conditions, and generalizable across those who have substance use disorder.

3 Objectives and Purpose

3.1 Primary Objective

- To evaluate the effect of active DLPFC RS-tDCS to decrease the distress component of CUD in MS.
- To evaluate the effect of DLPFC tDCS to reduce cannabis use in MS.

3.2 Secondary Objectives

- To evaluate the presence of persisting benefits in distress through the 3-month follow-up.
- To evaluate the presence of persisting benefits in cannabis use through the 3-month follow-up.
- To evaluate the interactions between the dependent measures of the primary objectives. The interactions between the dependent measures will be evaluated to test the hypothesis that an RS-tDCS-related change in cannabis use metrics is linked to a change in distress.
- To evaluate the interactions between distress and cannabis use and the exploratory outcomes of cognitive and symptom measures.

4 Study Design and Endpoints

4.1 Description of Study Design

This randomized, double-blinded, parallel-arm, sham-controlled study will recruit n=52 female MS patients (target is 42 patients plus 10% to account for screen fails and withdrawals) to be randomly assigned using a 2:1 randomization method to receive 20x20 min sessions of either active 2.0mA tDCS or sham tDCS, combined with simultaneous mindfulness meditation over a 4-6 week period. Groups will be matched on years of cannabis use (4 years or less vs. 5 or more years).

All participants will have a remote consent/research screening visit, baseline visit, 20 tDCS treatment visits, and 1-month, 2-month, and 3-month follow-ups. All visits will be completed remotely through Zoom or Webex. Study procedures will be the same for both groups, with the only difference being the tDCS stimulation setting of 2.0 mA active or sham.

This will be a single site study at NYU Langone Health and will take place over a 2 year period.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

- Change in distress measured by Kessler Psychological Distress Scale (K10) and Positive and Negative Affect Schedule (PANAS) between baseline and treatment-end.

- Change in cannabis use measured by Timeline Followback Method Assessment (TLFB), Marijuana Craving Questionnaire (MCQ-17), Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis-Use Inventory (DFAQ-CU) and Cannabis Withdrawal Scale (CWS) between baseline and treatment-end.

4.2.2 Secondary Study Endpoints

- Change in distress measured by K10 and PANAS across the 3-month follow-up to assess sustained improvement.
- Change in cannabis use measured by TLFB, MCQ-17, DFAQ-CU and CWS across the 3-month follow-up to assess sustained improvement.
- Evaluate the relationship between change in cannabis use metrics and change in distress.

4.2.3 Exploratory Endpoints

- Interaction between change in depression and/or cannabis use and MS symptoms (SymptoMScreen) and cognitive measures (BICAMS, Cogstate Brief Battery).

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ages 21-65 (inclusive)
2. Female
3. Seeking treatment to reduce or discontinue current cannabis use (smoke/vape/ingest)
4. Current Cannabis Use Disorder per DSM-V
5. K10 score 10-35, inclusive (mild to high moderate distress)
6. Definite MS diagnosis, relapsing remitting (RRMS) subtype
7. PDDS score 0–7 (mild to moderate neurological disability, established to be able to complete procedures)
8. All medications stable for ≥ 1 month prior to enrollment and throughout the trial
9. Ability to understand the informed consent process and provide consent to participate in the study
10. Stable and continuous access to internet service, email (WiFi “hotspot” to be provided if needed)
11. Ability to use mobile devices
12. Fluent in English language (due to outcomes validated in English versions only)
13. WRAT-4 score ≥ 85

Inclusion criteria may be confirmed through medical records, screening assessments and self-report.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. MS clinical relapse or use of high dose of steroids in the past month
2. Adhering to prescribed medical marijuana use in accordance with clinician’s guidelines
3. Alcohol, tobacco, or substance use disorder other than cannabis
4. Primary neurologic, psychiatric or other medical disorder other than MS
5. Currently meets DSM-V criteria for moderate or severe substance use disorder in the past 6 months for any psychoactive substance.
6. Meets DSM-V criteria for current panic disorder, obsessive-compulsive disorder, post-traumatic stress syndrome, bipolar affective disorder, schizophrenia, dissociate disorders, and any other psychotic disorder or organic mental disorder
7. Current suicidal ideation or deemed to be of potential risk of self-injury
8. History of traumatic brain injury
9. Seizure disorder or recent (<5 years) seizure history
10. Metal implants in the head or neck
11. Enrolled in group or individual therapy for substance use disorder concurrent to intervention
12. Any skin disorder or skin sensitive area near stimulation locations
13. Pregnant or breastfeeding

*Exclusion criteria may be confirmed through medical records, screening assessments and self-report***.**

5.3 Vulnerable Subjects

Vulnerable subjects will not be enrolled in this study. MS patients do not require additional cognitive screening to determine capacity to consent beyond the process described in section 13.3.2.1. Dr. Charvet PhD, is a practicing clinical neuropsychologist who specializes in the treatment of cognitive symptoms of

MS. MS can affect cognition mildly, however it is rare for MS patients to present with global cognitive impairment that would impact their capacity to provide informed consent.

5.4 Strategies for Recruitment and Retention

The MS Comprehensive Care Center (MSCCC) at NYU Langone Health has an extensive recruitment base. Patients who are seen by NYU medical staff, who fit the eligibility criteria, will be referred for the study by the study PI and sub-investigators. All physicians and medical staff at the MSCCC will be presented with the study description.

A patient who is seeing one of these medical staff members as their treating physician will be introduced to the study by that medical staff member. If the patient is interested and agrees to be contacted, a team member will contact them on the phone (or in-person if participant is already in clinic) using an IRB-approved phone script to provide additional study information and pre-screen to assess eligibility. Verbal responses will be recorded on a separate pre-screen verbal checklist. For any subject who is ineligible, or who is eligible but decides not to participate, we will immediately destroy the data collected during the pre-screen.

An IRB approved flyer will be posted in local physician offices and waiting rooms and throughout NYU, the surrounding community and support organizations. In addition to recruitment at NYU's MSCCC, we will post these flyers around the Ambulatory Care Center (ACC) for patients to recruit from the entirety of the Neurology department and from any number of people who come to visit the ACC on E38th Street or have an appointment at E41st Street.

An IRB approved study description will be posted on MS related websites and shared with appropriate list-services related to those websites.

BuildClinical marketing services will also be used to facilitate nationwide recruitment. Advertisements will be placed in various platforms. Prospective participants will click on the ad and be directed to the landing page to complete a screening form. A notification message will be sent to the study team upon completion of the form to review and connect with prospective participants.

5.5 Duration of Study Participation

Study participation will last approximately 4.5 months and will include:

- Remote consent (20 minutes), with participant provided as much time as they need to review consent form. Once consented, participant will be scheduled for telehealth research screening. The screening will be scheduled based on participant and study/clinician availability, which can occur on the same day as consent and anticipated to be within two days of consent.
- Telehealth research screening (1 hour).
- Baseline & tDCS Session 1 (approximately 2 hours: 20 minutes to orient to device, 1 hour assessments, 20 minute tDCS session).
- tDCS treatment sessions (20 x 20 min session over 4-6 weeks)
    - Sessions 5, 10, and 15 will be 45 minutes (20 minute session +25 minutes questionnaires)
- tDCS Session 20 & Treatment-end (1.5 hours)
- 1 month Follow-up (1 hour)
- 2 month Follow-up (1 hour)
- 3 month Follow-up (1 hour)

5.6 Total Number of Participants and Sites

Recruitment will end when approximately 52 participants are enrolled (sign consent). It is expected that approximately 52 participants will be enrolled in order to produce 42 evaluable participants.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.7.2 Handling of Participant Withdrawals or Termination

If a participant wishes to withdraw from the study they may do so at any point without adverse effect on their standard-of-care treatment. Participants will be provided with study team e-mail and contact number and can withdraw at any time

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Device Intervention

6.1 Study Device Description

tDCS is a device that delivers weak electrical current (2.0 mA) through sponge electrodes placed on the scalp. The main components are:

- **1x1 Mini CT tDCS device:** The device is powered by 9-volt (V) rechargeable batteries. The device can be easily operated, with a user-friendly large-button keypad interface. The device allows strict dose control and usage control, employing a one-time use code provided by the study technician to unlock the device for each stimulation session. The high sensitivity of the device to any changes allows us to monitor in real time the contact quality between the surface of the electrode and the skin ensuring safety and high quality of the delivered stimulation.

- **tDCS Headset:** The headset will be used to standardize and simplify the electrode placement. The headset uses two electrodes: the anode electrode and the cathode electrode. The DLPFC (anode over F3 and cathode over F4) electrode montage will be used to target the left prefrontal cortex. The headset connects to the tDCS device with two wires (anode and cathode).

- **Sponge electrodes:** The electrodes are square (5 x 5 cm^2) pre-saturated saline sponge electrodes packaged for single use equipped with snaps to fasten the sponges to the headset. The participant will be only required to open the package and snap the sponge onto the headset. The use of pre-moistened,

single-use electrodes avoids the possibility of over-saturating the sponge as this can saturate the hair, affecting the spread and the direction of the current flow.

tDCS is a non-significant risk device because it is:

1. not intended as an implant,
2. it is not purported or represented to be for use supporting or sustaining human life,
3. it is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise prevent impairment of human health and does not present a potential for serious risk to the health, safety, or welfare of a subject. tDCS has an established record of safety and tolerability for use from trials in a range of neurological and psychiatric condtions[106] [107], and including the specific remotely supervised and at-home use as proposed for this study[108] [109]. It has NSR designation for our trials specifically using the proposed procedures in participants with MS[110] [111] [112] [113] [114] [115] [116] as well as for use as an NYU Langone Health approval as innovative care for our tDCS clinical service program[117].
4. it does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

Attached is an NSR determination letter for FDA review of its use in a vulnerable population (developmentally disabled children).

6.1.1 Acquisition

The device will be provided by Soterix Medical Inc.

6.1.2 Product Storage and Stability

Devices, when not allocated to participants, are stored in-house in a locked room. Device allocation notes including device serial number and device unlock codes will be stored for reference.

6.1.3 Device Programming

To ensure blinding, devices will be pre-programmed in advance by an independent staff member, who will not take part in the treatment and assessment[118–120].

For active tDCS, the device is programmed to ramp up to 2.0 mA (for 30 seconds), provide constant current throughout session (19 minutes), and then ramp down (for 30 seconds) at the end.

For sham tDCS, the device is programmed to ramp up to 2.0 mA (for 30 seconds) followed by a ramp down (30 seconds), with no current delivery for 18 minutes, and then ramp up (for 30 seconds) and down (for 30 seconds) at the end.

6.1.4 Dosing and Administration

The tDCS device will deliver each session 2.0 mA for 20 minutes over the DLPFC. Participants will receive 20 intervention sessions over the course of this study on weekdays (M-F).

Study technicians are always live with participants via Zoom or Webex when initiating and delivering the treatment and can address any issues that arise during treatment. Study technicians will direct headset placement remotely. The tDCS device can only operate if: **1)** the headset is correctly placed for adequate connection, and **2)** the study technician provides a session code that unlocks the device for a one-time only 20-minute period of use.

If the device loses adequate electrode contact for any reason, the device will automatically discontinue the session. The session can only be reestablished if another unlock code is provided by the study technician. Specific stop criteria are outlined for treatment administration. Should any stop criteria be met at any point in administration of treatment, the participant will not undergo any further treatments and will be asked to return the study equipment (See Fig 3). If the participant wishes to discontinue a session, they may press the "abort" key at any time, which ramps down and stops the stimulation current within 30 seconds.

6.1.5 Route of Administration

tDCS is administered through a paired of sponge electrodes placed on the scalp using the headset. The device allows strict usage control, employing a one-time use code provided by the study technician to unlock the device for each stimulation session.

6.1.6 Duration of Intervention

Participants will complete 20 sessions of either active or sham RS-tDCS over the course of approximately 4-6 weeks. The tDCS will be programmed to deliver 20 minutes of stimulation.

6.1.7 Device Specific Considerations

- Device size: Height 7.2 in; Width 3.6 in; Depth 1.2 in
- Device model: Model 1601
- Device settings and programming: Double-blind option: Sham (ON/OFF), Secure administrator mode to program sessions, storage of data and codes of 250 sessions; SMARTscan to provide continuous visual indication of electrode quality during stimulation

6.2 Study Device Accountability Procedures

The device accountability and inventory log will be used to log device-use including subject ID, date shipped, dates used, session technician, and date returned.

7 Study Behavioral Intervention

7.1.1 Mindfulness meditation

The “10-Minute Mind” consists of guided mindfulness mediation audio tracks based on the “10 Minute Mind” program developed by Monique Rhodes. These guided mediations are built on the growing body of research for efficacy of mindfulness meditation for reducing psychological distress, including in CUD. Importantly, these audio tracks will be tailored specifically for use in this trial, to address both distress and cannabis use and timed to be paired to the 20 minutes period of tDCS. The 10 Minute Mind tracks will be downloaded on the laptop computer loaned to the study participants of both active and sham Arms.

7.1.2 Administration of Intervention

Participants will receive an laptop computer with the downloaded meditation audio tracks.

8 Study Procedures and Schedule

8.1 Study Procedures

After subjects provide written informed consent, the following research procedures will take place over approximately 4 months:

- A study clinician will conduct a telehealth research screening through Zoom, Webex or phone call to review patients’ medical history and confirm eligibility criteria. Ineligible patients may be referred for standard-of-care by the study clinician.

- If eligible, a study team member who is not involved in treatment delivery or assessment will randomize a device. The study equipment, including the tDCS device, headset, saline sponges, single panel cannabis test kit, and laptop computer will be shipped to the participant. The laptop computer will be pre-programmed with the meditation mindfulness programs.

- Baseline & tDCS Session 1:

- Following procedures for our validated protocol[85–89,91–95], participants will first receive training on the use of the tDCS device and headset.

- Participants will undergo a 90-second tDCS tolerability test to ensure the stimulation is tolerable. The participant will be given a one-time use code to initiate the stimulation, the tDCS device will ramp up to its target stimulation intensity (2.0mA) and after 90 seconds, participants will be instructed to press "0" to stop the test. Participants are free to stop the test at any time before the 90 seconds. Participants will then be instructed to remove the headset. Participants who cannot tolerate 2.0 mA will be considered a screen failure.

- Participants will be asked to complete a single panel cannabis test by following the instructions included in the test kit. This remote video method of urine strip testing has been used in other studies of participants with substance use disorders in rural communities[121]. Following these established protocols, the participant will be instructed to collect a urine sample in the collection cup (off camera) and then in view of the study technician will place a test strip into the cup and show the results. Participants will then be told to follow the disposal procedures included in the kit and wash their hands.

  While the remote connection does allow for a participant to provide a sample that is not their own to test, we believe that this occurrence would be of very low likelihood in this study sample. The participants are enrolled based on disclosed cannabis use, they are not incentivized in any way to decrease their cannabis use, and there would be no other primary or secondary gain for invalidating this procedure. Alternatively, in the similarly unlikely event that participants have falsely reported cannabis use and test negative at baseline, they will be withdrawn.

- Participants will complete self-report questionnaires about their physical and mental health, and cannabis use through REDCap survey function (see assessments section 8.2 below).

- For exploratory research, participants will complete cognitive measures (BICAMS, Cogstate Brief Battery) and MS symptom questionnaires.

- Participants will have their first 20-minute tDCS session of either 2.0mA active or sham tDCS combined with mindfulness meditation. At each treatment session, participants will complete brief adverse event reports before and after each session. Once the study technician visually confirms correct headset placement and participants confirms adequate contact quality (moderate or good), the technician will provide the participant with a one-time use unlock code to enter into their tDCS device. The participant enters the code when ready to initiate the stimulation. During each stimulation session participants will listen to a guided mindfulness meditation audio track on the study provided laptop computer.

- Remotely-Supervised tDCS Sessions 2-20:

  - Over the next 4-6 weeks, participants will complete the remaining daily tDCS + mindfulness meditations as described above for session 1.

  - After sessions 5, 10, and 15 participants will complete self-report questionnaires using REDCap survey function.

  - tDCS session 20 & Treatment-end: After completing the final tDCS session participants will repeat the baseline self-report questionnaires and measures, and the single panel cannabis test. Participants will be asked to return the equipment via Fedex using a prepaid return label.

- Post treatment-end follow-ups

Participants will have 3 follow-ups at 1, 2 and 3 months post treatment-end to repeat the questionnaires. At the 3-month follow-up the participant's will also be given a single panel cannabis test and asked a brief blinding integrity questionnaire (i.e. which group they think they were in) and then unblinded.

8.2 Study Assessments

8.2.1 Distress/Mood Assessments

- Kessler Psychological Distress Scale (K10)[121]: 10-item questionnaire intended to yield a global measure of distress based on questions about anxiety and depressive symptoms that a person has experienced in the past 4 week period.
- Positive and Negative Affect (PANAS)[122]: 20-item self-report questionnaire that measures positive and negative affect.
- Beck Depression Inventory (BDI)[123]: it is a self-report instrument intended to assess the existence and severity of symptoms of depression.
- State-Trait Anxiety Inventory (STAI)[124]: it is a psychological inventory based on a 4-point Likert scale and consists of 40 questions on a self-report basis to assess anxiety and trait anxiety.

8.2.2 Cannabis Use Assessments

- Timeline Followback Method Assessment (TLFB)[125]: self-report questionnaire to assess cannabis type and route of administration, frequency of use (number of days) and frequency of use during the day.
- Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis-Use Inventory (DFAQ-CU)[126]: 41-item questionnaire to measure frequency, age of onset, and quantity of cannabis used
- Marijuana Craving Questionnaire-17 (MCQ-17)[127]: 17-item questionnaire to assess marijuana craving.
- Cannabis Withdrawal Scale (CWS)[128]: scale to quantify the intensity of withdrawal symptoms, as well as the amount of distress or impairment in functioning due to each symptom.
- Cannabis Single Panel Test[54]: a single panel cannabinoid urine strip test will be used as secondary confirmation of the TLFB. Participant will be asked to collect a urine sample in a sterile urine sample cap right before the video visit. We will ask the participant to complete the test in real time through a live video connection with the study technician to verify and record the test strip reading. This strip test is made for the detection in human urine of cannabinoids and cannabis derivatives. The test is a qualitative assay (type "NO / YES"), and thus delivers a "negative" or "positive" result (cut-off: 50 ng/ml).
- The Cannabis Use Disorder Identification Test – Revised (CUDIT-R): 8-item screening instrument designed to identify potentially problematic or harmful recent cannabis use.

8.2.3 Cognitive and MS symptoms Assessments (Exploratory)

- Brief International Cognitive Assessment in MS (BICAMS)[129]: this battery includes tests of mental processing speed and memory including the Brief Visuospatial Memory Test (BVMT) and Rey Auditory Verbal Learning Test (RAVLT) and Symbol Modalities Digit Test (SDMT).
- SymptoMScreen[130]: 11-item tool to evaluate the symptom severity in domains commonly affected by MS.
- Cogstate Brief Battery (CBB): The core Cogstate RT tasks involve a deck of cards on a green background screen and the participant answers "yes" or "no" by hitting a keyboard key ("D" or "K") across repeated trials. Each task first includes instructions and practice period before the test begins.

8.2.4 Additional Assessments

- Wide Range Achievement Test (WRAT-4)[131]: an assessment to measure reading and comprehension skills.
- Patient Determined Disease Steps (PDDS): it is a patient-reported scale of disability in MS.

8.3 Study Schedule

8.3.1 Pre-Screening

- Team member conducts phone pre-screening (including WRAT-4, K10, and MS-PDSS) to determine general eligibility based on inclusion/exclusion criteria. Completing these measures over the phone is a practical option that helps screen out those who are ineligible before shipping study materials and it is suitable for phone use as participants can verbally respond to each scale.

  On the K10, those who score in the severe mental disorder range (36-50) will be offered to contact the NYU Langone Psychiatry Associates at (212) 263-7419, or if outside the NY area the Substance Abuse and Mental Health Services Administration (SAMHSA) hotline at 800-662-HELP (4357).

  All data collected for the purposes of the eligibility pre-screening will be destroyed immediately if the potential subject is ineligible or does not sign an informed consent form at their baseline.

8.3.2 Electronic Consent & Telehealth medical screening (Visit 1)

- Remote e-consent through SendSafe (*20 minutes*)
- Telehealth medical screen with the study clinician to review medical history and medication history [non-NYU patients may be asked to provide their medical records (e.g. fax to NYU study location)], and determine eligibility based on inclusion/exclusion criteria. (*1 hour*)
- Eligible participants will be scheduled for a baseline visit. A team member who is not involved in the administration of study procedures will randomize and program a tDCS device and study equipment will be shipped to participant.

8.3.3 Baseline Visit & tDCS Session 1 (Visit 2)

- Train participant to use tDCS device (20 *minutes*)
- Perform tDCS tolerability test (*2 minutes*)
- Perform the Cannabis 1 Panel Drug Test (*5 minutes*)
- Self-report questionnaires and measures (*1 hour*)
- Complete first remotely-supervised tDCS session *(20 minutes)*
  [First tDCS session and baseline questionnaires may be divided into two sessions +/- 7 days apart pending participant preference]

8.3.4 Remotely-Supervised tDCS sessions 2-19 (Visits 3-20)

- 20x20 minutes of active or sham tDCS with simultaneous mindfulness meditation (*20 minutes*)
- Self-report questionnaires will be administered through MyCap at sessions 5, 10, and 15 *(25 minutes)*
- AE reporting

8.3.5 tDCS Session 20 &Treatment-end Visit (Visit 21)

- Participants will complete tDCS session 20 (*20 minutes)*
- Repeat questionnaires and measures completed at baseline *(1 hour)*
- Perform the Cannabis 1 Panel Drug Test *(5 minutes)*
- Equipment return

[Last tDCS session and post-treatment questionnaires may be divided into two sessions +/- 3 days apart pending participant preference]

8.3.6 1, 2, and 3-month follow-up (months 2, 3, and 4, +/- 7 days) (Visits 22-24)

- Repeat questionnaires *(30 minutes)*
- Repeat cognitive measures and Cannabis 1 Panel Drug Test (only at 3-month follow-up) (3*5 minutes)*
- Unblind after completing 3-month follow-up and brief blinding integrity questionnaire

8.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

8.4.1 Precautionary Medications, Treatments, and Procedures

N/A

8.5 Prohibited Medications, Treatments, and Procedures

Treatment with medical cannabis will not be permitted for the duration of this study.

8.6 Participant Access to Study Agent at Study Closure

N/A

9 Assessment of Safety

9.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

9.1.1 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the

other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

9.1.2 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

9.1.3 Reporting of Pregnancy

Women who are pregnant or breastfeeding as determined by participant self-report or medical record will not be included in this study. Women who cannot confirm their pregnancy status via self-report or medical record will be excluded.

9.2 Classification of an Adverse Event

9.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

9.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study device is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship

to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- ***Related*** *– The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.*

- ***Possibly Related*** *– The AE may be related to the device. However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.*

- ***Not Related*** *– There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.*

9.2.3 Expectedness

Dr. Charvet will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

9.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of

cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

9.4 Reporting Procedures – Notifying the IRB

9.4.1 Adverse Event Reporting

Adverse event rates will be calculated and reviewed at DSMP meetings. Adverse event rates will be reported to the IRB as described previously. Should adverse event rates exceed the normal rates observed in the literature, the study PI will place the study on hold and review the safety of the study.

9.4.2 Serious Adverse Event Reporting

Serious adverse events that are related to the study device or interventions will be reported to the IRB within 24 hours of becoming aware of the occurrence.

9.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor within 5 business days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 10 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 10 business days of the IR's receipt of the report of the problem from the investigator.

9.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form,

and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in Section 1, Key Roles.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

9.6 Study Halting Rules

There are no predetermined stopping rules.

9.7 Safety Oversight

9.7.1 Data Safety Monitoring

It is the responsibility of the Principal Investigator to oversee the data safety monitoring of the study at his/her site. Data safety monitoring meetings will occur with every 10th subject enrolled (beginning when first participant is enrolled) and will include careful assessment of research procedures including protocol adherence, regulatory documentation, enrollment (e.g. rate of enrollment, screen fails, withdrawals), unanticipated problems, and any issues that may arise during the course of research. There are no predefined stopping rules.

Meetings will be documented in data safety monitoring reports (DSMR). An annual DSMR will be submitted to the IRB at the time of continuing review. This data safety monitoring will include careful assessment (e.g. frequency, relatedness, and expectancy) and appropriate reporting of adverse events (e.g. skin tingling, itching, warming, irritation) as noted above. Each tDCS administration will occur in the context of a live video visit through Zoom or Webex. With this real-time supervision of treatment, risk will be systematically monitored and minimized.

9.7.2 Medical Monitoring

Dr. Lauren Krupp, MD, Director of the NYU Langone MSCCC, will serve as medical monitor for this study. Dr. Krupp will be responsible for resolving any clinical matters that may arise, including careful assessment of the number and type of serious adverse events, determining relatedness to the research, and resolution.

9.7.3 Clinical Monitoring

N/A

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

Study data will be collected through REDCap survey function, and this records will be printed and stored in locked cabinet only accessible to the research staff. While survey data is collected via REDCap, no data will be stored in REDCap. All data will be destroyed from REDCap after it is transferred for storage. The identified data will shared with the BERD component of the Clinical and Translational Research Institute at Wake Forest School of Medicine for analyses purpose.

10.2 Statistical Hypotheses

We will test the hypotheses that there is an interaction between treatment (active vs. sham) and time on 1) distress (K10 & PANAS-NA) and 2) use (TLFB), with additional outcomes addressing mood/anxiety (BDI, STAI), detailed cannabis use (DFAQ-CU), craving (MCQ-17) and withdrawal (CWS).

If the interaction effect for an outcome is significant, we will conclude there is statistical evidence of overall treatment effect. If the spaghetti plots suggest trends (e.g., linear, quadratic, or piecewise changes) we will treat time as a continuous variable and fit repeated measures regression models along with group and its interaction with continuous time as independent variables.

In supplementary analyses, additional factors or covariates will be included in the models (along with their corresponding interactions with group and time) to examine the potential influence of gender, age, MS disability (PDDS), depressive symptoms (BDI), anxiety (STAI) and CUD severity (CUDIT-R) on responsiveness to active vs. sham treatment.

10.3 Analysis Datasets

Intent-to-Treat Analyses: All analyses will be performed on two samples: 1) the intent-to-treat sample consisting of all randomized subjects (n=52) and 2) the Per Protocol sample (individuals that completed all 20 sessions).

10.4 Description of Statistical Methods

10.4.1 General Approach

Prior to formal statistical analysis, summary statistics for all variables will be obtained and graphical displays will be generated (e.g., spaghetti plots, boxplots). All behavioral outcome measures will be based on standardized composite scores from the literature. These analyses will be used to identify potential heterogeneity and imbalance of randomization into the intervention arms within strata.

All baseline characteristics will be evaluated and considered for inclusion as covariates in the supportive and secondary comparative analyses based on baseline differences among treatment groups and clinical importance. We will also use data reduction techniques (such as factor analysis or principle component analysis) to confirm the applicability of the composite scores in our population.

10.4.2 Analysis of the Primary and Secondary Endpoint(s)

The efficacy of RS-tDCS to effect the outcomes of each Aim 1 & 2 will be tested using linear mixed effects models. The dependent measures (K10 score, NA, percent of days of use, CWS, MCQ-17) will be nested within timepoint (Visit 1, 5, 10, 15, 20), with active/sham as fixed effects. This will be done using the Matlab function ‘fitlme’ with REML estimation predicting change from V1 values following each 5 session RS-tDCS interval (Matlab, R2020a, The MathWorks Inc.).

Given that the purpose of this pilot study is to develop effect sizes for a subsequent R01, we will also derive least-squares means effect sizes of our research strategy on distress, NA, percentage of days of use in 4 intervals [V1-V5; V6-V10; V11-V15; V16-V20]. The number of days that elapsed in each interval will be used as a covariate.

10.4.2.1 Missing Data

We will perform attrition analyses on whether participants and dropouts differ on key variables (severity of cannabis use disorder or CUD, as measured by the CUDIT-R) and whether variables on which they differ interact with treatments to affect outcome measures. As participants will be randomized to treatment, it is unlikely that missing data will produce biased estimates of treatment effect, as observed and unobserved covariates should theoretically be balanced across treatment groups. Larger proportions of data missing at random (MAR) or missing not at random (MNAR) could potentially bias study findings and reduce power. Should substantial proportion of cases (over 10%) for a critical independent variables and evidence of non-randomness, missing data will be incorporated using multiple imputation methods and inverse probability weighting. Results will be examined in patients who completed at least one of their randomized assigned intervention sessions as supportive analyses. First the distribution of the missing indicator variable given the observed data is modeled to derive a propensity score. Then observations are grouped on these propensity scores and an approximate Bayesian bootstrap multiple imputation is applied to each group. This has previously been identified as a fruitful method in other addiction treatment research [Witkiewitz et al., 2015, *Addiction*, “Pain as a predictor of heavy drinking and any drinking lapses in the COMBINE study and the UK Alcohol Treatment Trial”].

10.4.3 Safety Analyses

The tolerability of the RS-tDCS system will be assessed by both the Adverse Event Report frequency (which will be compared with Fisher's exact test with active and sham as categories, and the mean cumulative function (MCF) for analyzing multiple/repeated occurring AEs to subjects during the treatment period), and participant retention in the study.

10.4.4 Adherence and Retention Analyses

Compliance with the interventions will be assessed by summarizing the distributions of numbers and proportions of completed sessions by intervention group. Supportive analyses will evaluate the effects of compliance on results for the primary outcome of change in distress from baseline to end of treatment. Compliance measures will be incorporated into the primary outcome of Aim 1 (distress) analysis models to estimate the effect of compliance on the primary outcome.

10.4.5 Planned Interim Analysis

N/A

10.4.6 Exploratory Analyses

We will collect exploratory cognitive and symptomatic measures towards our ultimate objective of evaluating its effects on disease burden. Exploratory outcomes of cognitive (BICAMS, Cogstate Brief Battery) and symptoms (SymptomMScreen) measures will be evaluated in a manner similar to that described above for the primary outcome.

10.5 Sample Size

Power analyses were conducted independently for Aim 1 and Aim 2, wherein estimated effect sizes came from 2 independent manuscripts that used tDCS to measure changes in distress (Aim1) and estimated changes in cannabis use (Aim 2). In the planned study subjects will be assessed at 5 time points with the Change from V1 being used as a dependent variable (4 pieces of data per dependent measure per participant).

There is an anticipated interclass correlation coefficient (ICC) of 0.8 for the within-subjects measures. The design effect which accounts for multiple correlated observations within each subject, is estimated to be 4.2 (DE= [1+(5-1) 0.8]. In a clustered setting, the sample size is $N_{effective}$ = nm/DE where n is the number of subjects required when m replications within participants are performed after accounting for the design effect (DE). The estimated number of individuals needed to detect an effect in the active RS-tDCS group is 28 for Aim 1 and 15 for Aim 2 (1-sided alpha of 0.05 and power of 80%).

For this study, we will utilize a 2:1 randomization based on pragmatic considerations including timeline, cost, and the added value of over recruiting to the Active group in order to have a better assessment of safety and tolerability data. In corporation this information into the total planned recruitment size, we arrived at n=42(=50 * 4.2 / 5). (28 allocated to active, 14 allocated to sham). We anticipate enrolling 52 participants which includes 10% drop out rate.

10.6 Measures to Minimize Bias

10.6.1 Enrollment/Randomization/Masking Procedures

In this pilot RCT, participants will be randomized 2:1 into one of two intervention groups consisting of active (Group 1) vs. sham (Group 2) tDCS paired with mindfulness meditation practice. A study team member who otherwise will not be involved in administering research procedures will randomize the device and keep the assignments in confidentiality (e.g. password protected spreadsheet).

During a sham session, the device is programmed to ramp up to the desired intensity (2.0 mA) and ramp down for the initial 60 seconds, with no current delivery during the session aside from the 60 seconds in the beginning and then again at the end of the session. These brief periods of stimulation serve to mimic the effects of a true stimulation session.

Randomization: We will stratify randomization by years of cannabis use (4 years or less vs. 5 or more years). Urn randomization will be used to balance the randomization assignment with respect to these strata. The purpose of stratification is to distribute this potential prognostic factor equally across treatment groups.

10.6.2 Evaluation of Success of Blinding

The integrity of the blind will be evaluated through a questionnaire that asks each individual 3 questions:

1) Do you think you are receiving active or sham tDCS?
2) Please write a brief sentence stating why you believe that to be true.
3) How confident are you (scale 1-10)?

The answers to Questions 1 & 3 will be entered into a non-parametric test of equality of proportions with confidence being a weighting variable and active or sham tDCS as a classification variable. The data from the written sentence will be used qualitatively for research presentations and provide insight into the participant experience.

10.6.3 Breaking the Study Blind

There is no plan to break the study blind prior to the 3 month follow-up unless there is an SAE or as required by NIH or NYU IRB.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, and subject files. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is

not applicable to the individual case, write “N/A”. All entries should be printed legibly in black or blue ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable NYU IRB regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 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.

13.2 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.

13.3 Informed Consent Process

13.3.1 Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study device, 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: informed consent form.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their relatives or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Subjects will be emailed a PDF version of the protocol and the phone number of a study team member to call after they have reviewed the consent. The study team member will then explain the consent to the subject, and ask if the subject has any questions. If the subject agrees to participate, they will electronically sign the informed consent document and email it back to the study team. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record.

13.3.2.1 Capacity to Consent

Based on Dr. Charvet's clinical practice and research, our study population is not expected to have significant cognitive impairment. Subject capacity to provide informed consent will be determined by trained team members or PI who will ask the participant open-ended questions regarding their understanding of key research information. All team members will be trained in GCP-ICH guidelines and will receive additional training by the PI or an experienced study team member. Reading comprehension will be assessed using the WRAT-4 and participants must score ≥ 85. A licensed clinician will not be required to ask the questions below or administer the WRAT-4 which has normative values.

Questions will include:

- In your own words, can you please explain the purpose of this research?
- What does it mean that your participation is voluntary?
- What happens if you sign consent and then later change your mind?
- What are the risks and benefits of participating in this study?

Reasonable judgement may be used to determine whether a participant's responses reflect proper understanding of key research procedures. Patients who do not answer these questions adequately will be excluded from the study. Continued capacity assessments are not required as cognitive decline associated with MS progresses over years so we don't expect any subjects will lose capacity over the course of 4.5 months.

13.4 Posting of Clinical Trial Consent Form

N/A

13.5 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.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13.5.1 Research Use of Stored Human Samples, Specimens, or Data

N/A

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

The self-reported questionnaires will be administered through REDCap survey function providing access to secure online questionnaires that can be completed from any browser. All study data collected through REDCap will be printed and stored in locked cabinet only accessible to the research staff at 222 E 41st Street, 10th Floor.

14.2 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.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents and reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 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 postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

This study will be funded by a grant from the National Institute of Health.

15.2 Costs to the Participant

Participants will not be responsible for any costs related to the research procedures involved in this study.

15.3 Participant Reimbursements or Payments

Participants will be compensated $250 for completing the study ($50 Baseline; $100 at treatment-end visit, $100 after the 3rd follow-up).

16 Study Administration

16.1 Study Leadership

Leigh Charvet, Ph.D.

Dr. Charvet is a professor of neurology and the Director of MS Research for the NYU Langone Health's MS Comprehensive Care Center, also directing the neuromodulation research program and clinical tDCS service. She has >25 years of clinical and research experience working with people living with MS. She has established a large research and clinical program using noninvasive brain stimulation with tDCS, and pioneered the development and validation of the remotely supervised, or RS-tDCS, tele-platform for interventions to be accessed by patients and research participants from home. She has an extensive record of funding for investigator initiated clinical trials including those supported by the NIH, National MS Society, U.S. Department of Defense and other agencies. Dr. Charvet will be responsible for overseeing

the completion of the research project, building on her extensive background in MS clinical trials, tDCS, and telerehabilitation. She will oversee all aspects of the study including procedures, recruitment, and tDCS intervention. She will coordinate the full study team with frequent contact and weekly meetings to successfully complete this trial. She will work with the study team to operationalize the study procedures and train all personnel in the procedures. She will work with study physicians to diagnose and screen participants at study entry. Dr. Charvet will exclude participants who are ineligible due to the presence of severe distress (K10), psychiatric comorbidity and/or suicidality (based from screening diagnostic interview). She will follow standard of care procedures which will include referral to additional mental health resources. She will lead participant recruitment, database creation, and data entry. She will monitor recruitment, and take the primary scientific responsibility for completing progress reports as well as presentation and publication of the study results. At study end, Dr. Charvet may refer participants to resources if they wish to continue management of cannabis discontinuation.

Giuseppina Pilloni, Ph.D.

Dr. Pilloni is a biomedical engineer with the therapeutic applications of noninvasive brain stimulation and tDCS devices, with extensive and international experience working in MS rehabilitation. She will provide biomedical engineering expertise for all equipment use. She will specifically oversee the collection of the primary outcome measure, and its recording and interpretation. Dr. Pilloni will coordinate all equipment, including ensuring the separate tDCS device programming for confident blinding. Drs. Pilloni, Charvet, and Hanlon will work with the vendors to ensure ongoing technical and equipment support and guidance for the trial.

R. Erik Charlson, M.D.

Dr. Charlson is an MS specialist and dual neurologist and psychiatrist and NYS certified marijuana practitioner. He brings his extensive clinical expertise to this project. He will work closely with the PIs to diagnose and screen participants at study entry. He will oversee intervention and participant status throughout the trial in his role as study physician, and provide clinical direction (standard of care) for any clinical issues that may arise. Dr. Charlson will exclude participants who are ineligible due to the presence of severe distress (K10), psychiatric comorbidity and/or suicidality (based from screening diagnostic interview). He will follow standard of care procedures which will include referral to additional mental health resources. At study end, Dr. Charlson may refer participants to resources if they wish to continue management of cannabis discontinuation.

Lauren Krupp, M.D.

Dr. Krupp is the director of the NYU Langone MS Comprehensive Care Center and will help support recruitment, publicize the study across the MS community, provide resources as needed to ensure the study's success, and provide assistance to Dr. Charlson by directing eligible patients to him for screening and enrollment. An internationally recognized expert in MS, with extensive experience on the use of tDCS in MS, she has served as Co-I and study physician for all RS-tDCS trials in MS to date. She will continue in this role as a physician monitor and advise regarding tDCS treatment issues as they relate to MS care. She will work closely with the PI and MS Center physicians to help with recruitment and will work to inform the local MS community about the study. She will participate in weekly research meetings, advise study clinicians regarding eligibility criteria with respect to aspects related to MS and tDCS and be available to help address issues related to tolerability as experienced during the trial.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NIH

has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

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19 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.

- Eligibility Checklists
- Verbal Screen Checklist

20 Schedule of Events

	Screening	Baseline	RS-tDCS sessions + mindfulness							Treatment End	Follow-up (month)		
			1-4	5	6-9	10	11-14	15	16-20		1	2	3
Study Team Procedures													
Obtain written informed consent	X												
Obtain medical history	X												
tDCS Device Training/tolerability test		X											
Assessments													
WRAT-4	X												
PDDS	X									X			X
K10	X			X		X		X		X	X	X	X
PANAS		X		X		X		X		X	X	X	X
TLFB		X		X		X		X		X	X	X	X
Cannabis Single Panel Test		X								X			X
DFAQ-CU		X								X	X	X	X
MCQ-17		X		X		X		X		X	X	X	X
CWS		X		X		X		X		X	X	X	X
BDI		X								X	X	X	X
STAI		X								X	X	X	X
CUDIT-R		X								X	X	X	X
Exploratory cognitive and symptom measures													
BICAMS		X								X			X
Cogstate Brief Battery		X								X			X
Symptom MS Screen		X								X			X
Safety Reporting													
AE reporting			X	X	X	X	X	X	X				