PARTNERS HUMAN RESEARCH COMMITTEE DETAILED PROTOCOL

DETAILED PROTOCOL: Evaluation of Medical Cannabis and Prescription Opioid Taper Support for Reduction of Pain and Opioid Dose in Patients with Chronic Non-Cancer Pain
Principal Investigator: Jodi Gilman, Ph.D., A. Eden Evins, MPH, M.D.
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I. BACKGROUND AND SIGNIFICANCE

Approximately 50 million adults in the United States suffer from chronic non-cancer pain (CNCP), a debilitating medical condition that is among the most complex to manage [1]. Though nearly 90% of those with CNCP are treated with chronic opioid therapy (COT) [2], the evidence supporting effectiveness of chronic opioid analgesics to improve pain and functioning is weak.[3] Further, use of COT for CNCP has contributed to an epidemic of opioid use disorder (OUD) [2, 4, 5]. In 2016, more than 80,000 individuals died from an opioid overdose in the US [4, 5]. Moreover, in pain clinics, those treated for CNCP have opioid misuse and OUD prevalence of 8-16% and 2-14% respectively [6, 7]. Opioid misuse and OUD significantly increases mortality risk [6, 8] in a dose related manner. The 2016 CDC Guideline for Prescribing Opioids for Chronic Pain [9] recommended several strategies to mitigate these risks of using COT for chronic pain, including 1) prescribing the lowest effective dose, and avoiding escalations of dose above 90 MME/day, and 2) tapering opioids when the risks exceed the benefits. The limited available evidence about outcomes of PO tapering suggests that pain and functioning often improve and do not worsen with opioid dose reduction [10, 11]. Though converging evidence has led to a consensus that COT dose reduction generally improves pain, function, and quality of life in those with CNCP [10], and also reduces risk of OUD and opioid overdose deaths, optimal strategies for reducing opioid dose in real-world settings are largely unknown [12].

The cannabinoid CB1 and CB2 receptors of the endocannabinoid system modulate pain-processing pathways [13, 14]. CB2 receptor agonists indirectly stimulate opioid receptors located in primary afferent pathways [15], and therefore, in addition to their direct analgesic effects that are independent of opioid receptor activation, it has been hypothesized that cannabinoids may work synergistically with opioid analgesics to reduce pain. Initial pre-clinical studies have been promising, as animal models have identified a role for CB1 receptor activation in reducing neuropathic, visceral, and inflammatory pain [16], and several pre-clinical studies have suggested that systemic use of cannabinoid receptor ligands produces analgesia in acute and chronic pain models [17]. A meta-analysis of 19 pre-clinical studies (with acute-dosing paradigms) demonstrated that combining a cannabinoid with an opioid produced a synergistic analgesic effect, better than each individual drug alone [18]. Human laboratory studies also indicated that cannabidiol (CBD), a constituent of medical marijuana (MM), may reduce craving for opioids in those with OUD [19, 20].

As of May 2020, MM has been legalized in 33 states and Washington, D.C. MM began to be conceptualized as a 'substitute' for opioids following a report that states with legal MM had lower-than-expected opioid overdose (OOD) mortality rates from 1999 to 2010 [21]. Without further evidence for efficacy, MM was approved by several states as a treatment for OUD [22]. A reanalysis of the state level data, with longer duration of data collection (through 2017), reported the opposite result; rather than a 21% lower than expected OOD rate, the new analysis with more data showed states with MM had a 23% increased rate of OOD [23]. Further, a recent 4-year, longitudinal study of CNCP patients found that MM use among those on opioids neither improved patient outcomes nor exerted an opioid-sparing effect (an effect whereby co-administration of MM with opioids would enable opioid dose reduction without loss of analgesic efficacy) [24]. In contrast, a report of a single-site retrospective cohort study claimed that among 180 patients with chronic low back pain on COT, half stopped all opioid medications and a further 31% reduced their opioid dose after starting MM [25]. Despite limited and controversial evidence for MM efficacy on COT [26], chronic pain is the most common reason that individuals seek MM cards [27], many adults with CNCP are trying MM to try to improve their pain and functioning and to reduce opioid doses and are asking clinicians for guidance.

Rationale behind the proposed research, and potential benefits to patients and/or society

There are no published reports of randomized trials of MM effectiveness for reducing opioid dose. Findings from clinical trials on the effectiveness of cannabinoids for chronic pain are inconsistent and

most studies have serious limitations, such as lack of control conditions. A 2018 Cochrane review[26] examined 16 studies involving 1750 individuals and concluded that "there is a lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain." This review included studies of oromucosal spray with a plant-derived combination of tetrahydrocannabinol (THC) and cannabidiol (CBD; 10 studies), a synthetic cannabinoid mimicking THC (nabilone; 2 studies), inhaled herbal cannabis (2 studies), and plant-derived THC (dronabinol; 2 studies). A 2017 review by the Department of Veterans Affairs similarly concluded that there was insufficient evidence of the efficacy of cannabis for populations with chronic pain (though they determined that evidence suggested cannabis may alleviate neuropathic pain) [28]. Yet, a 2017 report from the National Academies of Sciences, Engineering and Medicine (NASEM) concluded that there was "conclusive or substantial evidence" that cannabis is effective in treating chronic pain, though this report did not separate different types of pain in this analysis [29]. The most consistent evidence for the effectiveness of cannabis is for neuropathic pain [30-33], though this clearly needs further study.

Healthcare providers are increasingly confronted with patients who are interested in using MM to treat various disorders, especially CNCP, and evidence-based studies do not exist to offer guidance regarding risks of addiction, basic use behavior, or side effect profiles of MM. In contrast to medicines that undergo FDA review, MM lacks basic information about safety, efficacy, and adverse effects. Evidence to support the effectiveness of MM for chronic pain is controversial [34], and evidence for MM to treat OUD, or even to promote successful opioid tapering, is virtually non-existent [24]. Moreover, data is lacking on whether those who use MM for chronic conditions develop similar rates of addiction to those who use cannabis for recreational purposes. The most recent US national data reports that 3 out of 10 cannabis users develop CUD, and 23% of these are symptomatically severe (≥ 6 CUD criteria) [35]. Cannabis users also develop physical dependence on the drug, reporting tolerance to many of the effects of THC [36, 37]. Thus, controlled trial data is critically needed to evaluate opioid sparing claims in this population, and to assess impact of adding MM to COT on pain, symptoms of OUD, other SUD, cognition, and other outcomes that are critical to this decision-making.

This will be the first randomized, pragmatic trial to test whether MM use by adults on high-dose COT for CNCP is associated with reduced opioid dose and improved pain severity when added to a behavioral intervention. Results will provide critical information to patients and providers about potential benefits, as well as unintended consequences, of using MM to treat chronic pain, a practice that is widely publicized as effective and low risk. This study will provide data to help patients and providers weigh risks and benefits of MM and make more informed treatment decisions.

II. SPECIFIC AIMS

The goal of this proposal is to assess whether MM, when added to a 24-week behavioral prescription opioid taper support (POTS) program that has been shown to support safe opioid dose reduction without worsening of pain, reduces opioid dose and improves pain intensity and interference in adults on COT for CNCP, more so than POTS alone (without the addition of MM).

Aim 1: Evaluate whether adults with CNCP on COT assigned to MM+POTS, compared with those assigned to WL+POTS, have greater reduction in opioid dose (MME/day), and/or greater improvement in pain intensity and interference (PEG Scores) from baseline to 24 weeks *(co-primary outcomes*). These outcomes will be assessed via daily diaries.

Aim 2: Evaluate whether participants assigned to MM+POTS, compared with those assigned to WL+POTS, have improved quality of life, depression, and anxiety; and improvement in cognitive functioning (e.g., memory, attention, executive function). These outcomes will be evaluated through assessments and cognitive tests including the California Verbal Learning Test (CVLT)-3, Conner's Continuous Performance Test (CPT)-3, and the Weschler Adult Intelligence Scale (WAIS)-IV Digit Span Task.

Aim 3: Evaluate whether those assigned to MM+POTS develop symptoms of CUD over the 24-week intervention, as well as at the 12-month time point. This will be assessed by the DSM-5 Cannabis Use Disorder Checklist. We also plan to evaluate whether those assigned to MM+POTS have a reduced number of OUD symptoms (DSM-5 OUD Checklist) at 24 weeks compared to the WLC.

This is a multi-site trial. Cambridge Health Alliance (CHA) and Maine Medical Center (MMC) will be engaged in conducting the same study procedures as MGH and will rely on the oversight of the MGB IRB.

III. SUBJECT SELECTION

Inclusion Criteria:

1. Men and women aged 18-75, inclusive.
2. Endorsing > 6 months of CNCP
3. On stable prescription opioid doses of ≥ 25 MME/day for >90 days.
4. Either no prior use or current light cannabis use **(**weekly or less in the past 12 months).
5. Plans to use medical cannabis for pain to control pain and/or reduce opioid dose.
6. Competent and willing to provide written informed consent in English.
7. Potential participants of childbearing potential must have a negative urine pregnancy test at enrollment and agree to use effective contraception: abstinence; hormonal contraception; intra-uterine device, sterilization; or double barrier contraception, during the study.

Exclusion Criteria:

1. Current cannabis use (including inhaled or ingested CBD products) of greater than weekly on average in the past 12 months, assessed via self-report (no more than 10 times in the last 90 days).
2. Current cannabis use disorder; moderate to severe substance use disorder for any substance (e.g., alcohol, cocaine, stimulant) by structured interview, EXCEPT nicotine and opioids (OUD).
3. Current uncontrolled major medical illness, such as cancer, cardiovascular disease, sickle cell disease, symptomatic hypothyroidism/hyperthyroidism or severe respiratory compromise.
4. Use of non-prescribed opioids, by self-report or urine toxicology screen.
5. Dose change or initiation of medications with significant analgesic effects (e.g., tricyclic antidepressants, SSRIs, gabapentin, NSAIDs) in the past 4 weeks.
6. Concomitant medications will be discussed at each visit, and any medications that may interact with cannabinoids (e.g., warfarin) will be discussed with a study clinician prior to enrollment or continued participation.
7. Actively suicidal and/or suicide attempt or psychiatric hospitalization in past year, or current suicidal ideation with specific plan or intent.
8. History of intellectual disability (e.g., Down's syndrome) or other severe developmental disorder or IQ < 70.
9. Current diagnosis of delirium, dementia, amnesia, or another cognitive disorder; current diagnosis of bipolar II disorder; lifetime diagnosis of a clinically significant personality disorder (e.g., borderline, antisocial, paranoid, schizoid, schizotypal, histrionic personality disorders); lifetime diagnosis of bipolar I disorder, schizophrenia spectrum or other psychotic disorder.
10. Surgery within the past month or planned during the next 6 months.
11. Pregnant or trying to get pregnant or breastfeeding.
12. In the opinion of the investigator or study physicians, not able to safely participate in this study.

Source of subjects and recruitment methods

Participants will be recruited through community advertising, accessing a cross-section of the population in Greater Boston, as well as advertising and physician referral from local MGH clinics, the MGB Healthcare network**,** the Cambridge Health Alliance healthcare system, and the Maine Medical Center healthcare system. Participants will also be recruited using the Research Patient Data Registry (RPDR) through MGB, a clinical data registry that can identify patients for clinical trials. We will run queries on EPIC and RPDR to find subjects with chronic pain on stable prescription opioid doses of ≥ 25MME/day for >90 days, meeting the eligibility criteria for this research study. Subjects identified through these mechanisms will receive a recruitment letter via Patient Gateway or by mail from study staff. The letter will not be sent to those who have opted out of receiving research invitations**.** Study staff will also use existing patient registries and lists to show primary care providers lists of their patients on chronic opioid therapy, with a nudge to mention the study to patients in

person or by letter. All advertisements will be IRB approved and will target people who are interested in obtaining MM who endorse >6 months of chronic non-cancer pain (CNCP), are on stable prescription opioid doses of ≥ 25 MME/day for >90 days and have no prior use or current light cannabis use (monthly or less in the past 12 months). Potential participants will complete a telephone screen for eligibility.

IV. SUBJECT ENROLLMENT

MGH Study staff will conduct telephone screening in response to a potential participant inquiry. A telephone screening will distinguish the majority of potentially eligible subjects from those not meeting eligibility criteria. This will consist of a brief discussion of the research study, confirming a potential participant's understanding of the basic study procedures, interest in participation and whether he/she meets eligibility criteria and includes asking for current medications, gender, age, pregnancy status, and history of psychiatric conditions including substance use disorders. Those not eligible for the experiment based on the phone screen will be informed that they do not qualify for entry into this particular study. Also note that participants who express interest in the study may be asked to complete a REDCap survey containing questions from the phone screen, instead of completing the screen via phone call.

All individuals who expressed interest in participating in the study and are potentially eligible based on the telephone screen will be scheduled for an in-person or remote enrollment visit to sign consent and complete eligibility screening procedures.

Procedures for obtaining informed consent

MGH staff will send the informed consent form to participants and will schedule them for an in-person enrollment visit. During the enrollment visit, the usual discussion of procedure, risks, side effects, confidentiality, voluntary participation, and right to refuse participation without prejudice will be explained to participants by a trained member of the study staff prior to administering any study procedures. All participants will be given the opportunity to ask questions to a doctoral-level member of the study staff during the consent process. Participants must be capable of understanding the nature of this study, its potential risks, discomforts and benefits before signing consent. Contact information of key MGH study staff will be provided to participants, they will be encouraged to ask any questions or concerns they may have about the study. All participants will be provided with a copy of their signed consent forms.

To comply with public health efforts to address COVID-19 and to expand access to diverse populations, virtual visits may be conducted as necessary. Virtual visits will be conducted via MGB approved platforms (i.e. video calls over Zoom and phone conferences via Cisco Jabber) and will mirror in-person visits with the identical personnel present on the call. All questionnaires typically collected during the in-person screening visit may be collected during the remote screening visit, as they are largely already completed on secure online platforms (i.e., REDCap).

If the screening visit is conducted virtually, informed consent will be obtained remotely. This will be done via electronic consent (e.g. MGB REDCap e-consent), or a remote consent process where the participant will be asked to sign the consent form and return back by email or mail. In either case, the consent discussion will occur identically to an in-person visit, but instead held over phone call or video conference. At the time of such visit, informed consent will be obtained by a trained member of the study staff with investigator back-up. All participants will be given the opportunity to ask questions to a doctoral-level member of study staff or an Investigator during the consent process. Following the informed consent process, a copy of the signed consent document will be provided to the patient (electronically if e-consent was used). In the case of e-consent, consent will be documented on MGB REDCap and through a Note to File for each subject for which it was obtained remotely. The REDCap e-consent template being utilized is equivalent to written consent and is both IRB approved and FDA compliant. As is with in-person consent, the study team will obtain and document informed consent before the participant is enrolled and any study procedures begin.

Treatment assignment, and randomization

Eligible participants will be randomly assigned in blocks of 6, to MM+POTS or WL+POTS. If we find that more patients drop out in the WL+POTS group, we will randomize, in blocks of 6, 1:2 MM+POTS: WL+POTS to achieve our goal of 100 patients completed in each arm by the end of the trial.

Randomization will be computer generated. Assessments will be conducted by study staff blind to the study intervention.

V. STUDY PROCEDURES

Participants who express interest in participating in the study will undergo a telephone screen to assess eligibility. If eligible, they will be scheduled for an in-person study visit, during which a consent procedure will be conducted with the study staff with a clinician available for questions, and a baseline assessment of questionnaires, cognitive testing, interviews, and laboratory assessments will be conducted and a random assignment will be made to MM+POTS or WL+POTS. Participants assigned to the MM+POTS group will be able to use MM without delay. Participants will be scheduled for repeat study visits at approximately 4, 8, 12, 16, 20, and 24 weeks. A follow-up phone call for all participants at approximately 1 year will assess for further long-term changes in our outcomes of interest. Our primary end point is the 24-week assessment.

a. Study visits and parameters to be measured

Screening Visit:

After a participant has met basic eligibility criteria over the phone, they will be scheduled for an enrollment visit at MGH where potential participants will be consented to the study based on procedures previously described under Procedures for Obtaining Informed Consent, and then further screened for eligibility.

The following procedures will take place after informed consent is obtained:

i. Medical history and assessment of current medical conditions, vital signs, height and weight.
ii. Collection of demographic information and family history.
iii. Neuropsychiatric Interview.
iv. Concomitant medication history to ensure that the participant is not taking any medications that may make them ineligible for the study.
v. Clinical ratings scales: DSM-5 CUD Checklist, DSM-5 OUD Checklist, TLFB (MJ, EtOH, nicotine, other drugs).
vi. Collection of a urine sample for a pregnancy test, a drug screen for amphetamines, cocaine, barbiturates, benzodiazepines, methamphetamines, opioids, and ethanol (though these will not be exclusionary).

Study staff approved to use the Prescription Monitoring Program (PMP) (study physicians and their delegates) will use the PMP to document statewide prescriptions for opioid medications and other medications monitored by the PMP doses. Study staff will use the electronic medical record to document concomitant medications prescribed by caregivers in the MGB, CHA, and MMC systems of care to improve the accuracy of and augment self-report of concomitant medications.

As part of study procedures, participants will be asked to share their participation in the study with their treatment team(s) and provide contact information for their prescribing physician to the study team. Study staff will contact the provider(s) primarily responsible for the participant's opioid prescribing at the time of enrollment to inform them of the participant's participation in the study, and again each time a new dose is agreed upon by the participant and the study team. Decisions regarding opioid dose adjustment are subject to approval by the prescribing physician.

Participants who give permission to receive text messages from the study staff will receive appointment reminders via text one week and one day before upcoming appointments.

Baseline visit to week 24:
Study visits will take place approximately at study weeks 0 (baseline), 4, 8, 12, 16, 20, and 24. Data collection at these visits will include: self-administered assessments, clinician-administered assessments, and a urine drug test. Some or all of these assessments may be done remotely according to COVID-19 requirements. Assessments will use standard, validated measures, selected for consistency with the PhenX Toolkit [38], the IMMPACT recommendations for chronic pain trials [39], and the NIH Research Standards for Chronic Low Back Pain [40], many of these items and scales are also PROMIS measures [41, 42]. Using these measures will improve data harmonization and the ability to interpret our findings in the context of other rigorous pain trials. Data collection at study visits will also include covariates including sociodemographic information (baseline) and clinical characteristics comprising pain type/location and duration on opioids (baseline) as well as current opioid dose and non-opioid pain medications or treatments (all study visits).

Follow up phone call (week 52):
At this phone call visit, we will administer the DSM-5 Opioid Use Disorder and Cannabis Use Disorder Checklist, a short neuropsychiatric Interview.

Obtaining MM: Participants can obtain MM at medical dispensaries or recreational shops. Participants can use any type of MM they chose; study staff will assess brands, amount used (days per week, times per day), method of use (smoke/consume), apparatus (bong/bowl/pipe, vaporizer, joint, blunt, edibles, dabs/wax, spliff, other), and potency of THC/CBD and other cannabinoids, if known. Participants will be responsible for the cost of the MM.

Time and Events Table

Measure	Instrument	Visit 0 Screen	Visit 1 Week 0	Visit 2 Week 4	Visit 3 Week 8	Visit 4 Week 12	Visit 5 Week 16	Visit 6 Week 20	Visit 7 Week 24	Week 52
Demographics	Custom (PhenX-based)	x								
Medical History	Custom (MedDRA, Review of Symptoms)	x								
Family History	Kiddie Schedule for Affecitve Disorders and Schizophrenia (K-SADS)	x								
Quality of Life	Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q_SF)		x	x	x	x	x	x	x	
	Patient Global Impression of Change		x			x			x	

Social Support	10-Item Social Provisions Scale (SPS-10)	x								
Pain	Brief Pain Inventory Short Form (BPI)	x	x	x	x	x	x	x	x	
Depression, Anxiety, Sleep	PROMIS-29		x	x	x	x	x	x	x	
	Beck Depression Inventory (BDI)	x								
	Beck Anxiety Inventory (BAI)	x								
	Pittsburgh Sleep Quality Index (PSQI)	x								
Cognitive Functioning	Conner's Continuous Performance Test (CPT)-3		x						x	
	California Verbal Learning Test (CVLT)-3		x						x	
	Weschler Adult Intelligence Scale (WAIS)-IV		x						x	
IQ	WTAR	x								
Cannabis Use Disorder	DSM-5 CUD Checklist	x	x			x			x	x
Opioid Misuse	Current Opioid Misuse Measure		x	x	x	x	x	x	x	
Opioid Problems	Prescribed Opioid Difficulties Scale		x	x	x	x	x	x	x	
Opioid Withdrawal Scale	Clinical Opioid Withdrawal Scale		x	x	x	x	x	x	x	
	Short Opiate Withdrawal Scale		x	x	x	x	x	x	x	
Substance use	Urine drug test	x	x	x	x	x	x	x	x	
Opioid Use Disorder (OUD)	DSM-5 OUD Checklist	x	x	x	x	x	x	x	x	x
Pain Impact	Pain Self-Efficacy Questionnaire		x	x	x	x	x	x	x	
Pain Catastrophizing	Pain Catastrophizing Scale		x	x	x	x	x	x	x	
Distress	Distress Tolerance Scale		x			x			x	
Pleasure	Snaith-Hamilton Pleasure Scale		x			x			x	
Delay Discounting	Monetary Choice Questionnaire	x							x	

Psychiatric Disorders	Neuropsychiatric Interview	x								
	Structured Clinical Interview for DSM-V Personality Disorders (SCID-5-PD; Borderline, Histrionic, Narcissistic personality disorders)	x								
ADHD	Adult ADHD Self-Report Scale (ASRS)	x								
Impulsivity	UPPS-PS	x								
Delusions/ Psychotic Experiences	Peters Delusion Inventory (PDI)		x						x	
Suicidality and Risk Taking	CHRT	x	x	x	x	x	x	x	x	
Experience(s) of Trauma	Brief Trauma Questionnaire			x						
Frequency of substance use	TLFB (MJ, EtOH, nicotine, other drugs)	x	x	x	x	x	x	x	x	
Alcohol Use	Alcohol Use Disorders Identification Test (AUDIT)	x								
Cannabis Use	Cannabis Use Disorders Identification Test (CUDIT)	x								
Nicotine Use	Fagerstrom Test for Nicotine Dependence (FTND)	x								
	Electronic Cigarette Dependence Index (ECDI)	x								
Adverse events (AEs)	Adverse Event Record		x	x	x	x	x	x	x	
Metabolites in Urine (only MM+POTS group)	Cannabis metabolites								x	
Concomitant Medication Changes	Concomitant Medication Record	x	x	x	x	x	x	x	x	
Opioid Dose	MME/day (daily)	x	x	x	x	x	x	x	x	
Pain Intensity and Interference	PEG (Pain, Enjoyment, General Activity) Scale (Range 0-30; daily)	x	x	x	x	x	x	x	x	

MM use	MM Use Frequency (daily)	x	x	x	x	x	x	x	x	
Readiness to Change	Readiness Ruler	x	x	x	x	x	x	x	x	

b. **Drugs to be used N/A**

c. Devices to be used: N/A

d. Interventions

Prescription Opioid Taper Support (POTS), a manualized behavioral prescription opioid taper support intervention developed by consultant, Dr. Judy Turner [11], will be offered weekly to all participants to support behavioral self-management of pain and structured, voluntary taper of COT dose. POTS has been validated for use in person, by phone, and videoconference. We plan to deliver sessions via videoconference or in-person. Sessions will be led by a trained clinician. There is no cost to subjects or their insurance for these sessions. With participant consent, POTS sessions will be video recorded to assess treatment fidelity.

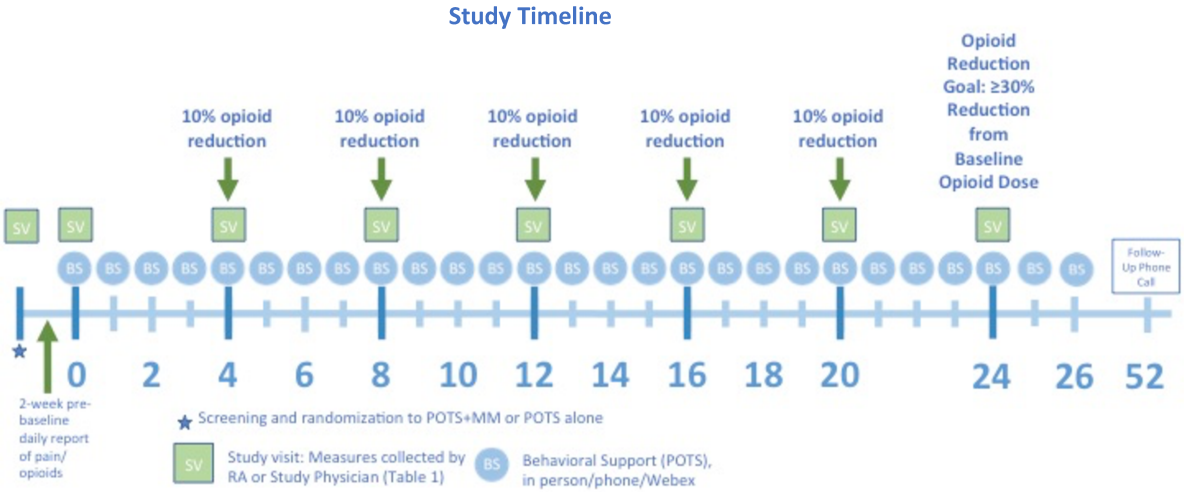
POTS sessions will be focused on individualized problem solving for behavioral self-management of pain and pros and cons of COT dose taper. During the 5 POTS sessions in study weeks 4-20 that coincide with the monthly study visits, study clinicians will work with participants to reduce opioid dose in increments of approximately 10% of the baseline opioid dose.

At the baseline visit, following consent, participants will be introduced to the process of opioid tapering. They will participate in a discussion of topics including:

1) describing their history of pain and benefits and difficulties with opioid therapy,
2) education on the health risks of high dose COT, and
3) identifying barriers that they may perceive to tapering opioid dose and strategies to overcome them.

Participants will be encouraged but not required to taper their opioid dose. At visits at (approximately) weeks 4, 8, 12, 16, 20, if the patient agrees, an opioid dose reduction as close to 10% of opioid dose at study start as is practical will be initiated, as reported by consultants Drs. Mark Sullivan and Judy Turner [11]. Participants can choose at any of these 5 visits to not decrease their opioid dose or to decrease their opioid dose by any amount agreed upon with their study clinician. The study clinician will not recommend an increase in opioid dose over their baseline dose. Participants who choose to increase their opioid dose will be transitioned to their primary care physician for dosing. All participants, whether or not they increase their opioid dose, will be encouraged to remain in the study and attend both POTS and monthly study visits and follow up visits, so their outcome data can be collected, and will be incentivized to do so.

Two POTS sessions will be conducted in weeks 24-26 to facilitate and coordinate return of care to the primary care physician, and the clinician will consult on adjunctive therapy that may be beneficial for pain control and maintenance of opioid dose achieved in the trial or continuation of dose taper. POTS sessions will not be focused on MM; clinicians will be instructed to neither encourage nor discourage MM use as they work to optimize behavioral pain management strategies. This is natural for this intervention, as its focus is on non-pharmacological approaches to pain and opioid dose taper.



e. **Data to be collected**

Dosing Diaries**.** We will collect data every day for approximately 26 weeks (plus approximately a 2-week pre-baseline period to establish levels of pain and symptoms) using a REDCap daily survey. The link will be sent via text message. Participants will be asked to enter a four-digit code prior to completing the survey to protect privacy, and participants will have the opportunity to opt out of receiving text messages. Participants will be asked to keep a daily log of (1) opioid dose (MME/day), (2) pain, which will be assessed with the Numeric Rating Scale (NRS) which is used to assess pain level on an 11-point scale (0 = no pain, 10 = worst pain imaginable), (3) MM use, and (4) ratings of sleep quality, mood, and general health. To encourage daily reporting, participants will receive daily micro-reimbursements for reporting opioid/MM use in their dosing diaries, including no use. At the screening visit, we will teach participants to use the diaries and participants will be asked to begin completing the daily survey 2-weeks prior to their baseline visit.

Urine Testing. At all study visits participants will provide a urine sample, which will be qualitatively screened for substances such amphetamines, cocaine, barbiturates, methamphetamines, benzodiazepines, codeine, morphine, and ethanol, and will be quantitively screened for opioids. The urine sample will also be used to verify that those assigned to the WL+POTS condition are not using cannabis. In addition, participants in the MM+POTS group will provide a urine sample, which will be sent to the Pharmacy and Therapeutics Committee at the University of Colorado School of Medicine for a quantitative metabolite assay that will measure cannabis metabolites. Metabolites will be assessed at week 24.

For remote visits, participants will be asked to consent to shipping their urine samples to study staff for analysis of cannabinoid metabolites. Participants who consent will receive urine sample kits by mail after their screening visit, and prior to any subsequent remote visits. Kits include a sample cup, biohazard bag, packaging bag, UPS shipping bag, and detailed instructions on how to provide and package their urine sample. Participants will be instructed to leave the packaged sample at the location where their mail is picked up at their home before the scheduled pickup time. Study staff will schedule a UPS pickup for overnight shipping from the participant's home to the Center for Addiction Medicine office.

Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF) [43] is a 16-item self-administered questionnaire that captures life satisfaction over the past week. It will assess an individual's perceived general physical and mental health and has been shown to be both a reliable

measure of self-reported health and a powerful predictor of mortality and morbidity. It will be administered at all study visits.

Patient Global Impression of Change is a 7-point scale recommended by IMMPACT [39], to assess patient satisfaction with treatment at Weeks 0, 12, and 24.

Brief Pain Inventory (BPI)[44] interference subscale score (0 to 10) will assess pain impact (pain-related function) over the past week and is sensitive to change [45]. It will be administered at all study visits.

PROMIS-29 (v2.0)[42] is a well-validated measure recommended for use in chronic pain trials by both IMMPACT and the NIH Research Standards for Chronic Low Back Pain [39-42]. Three subscales will be administered at all study visits. The depression subscale assesses self-reported negative mood (sadness, guilt), views of self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose). The anxiety subscale assesses self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness). The sleep disturbance subscale assesses sleep quality.

Conner's Continuous Performance Test (CPT)-3 is a task-oriented computerized assessment of attentiveness. Score dimensions of inattentiveness, impulsivity, sustained attention, and vigilance will be measured at baseline (V1) and 24 weeks (V7). Normative data are available.

California Verbal Learning Test (CVLT)-3 is a comprehensive assessment of learning and memory for older adolescents and adults. The CVLT is considered to be the most sensitive measure of episodic verbal learning and includes standardized scores across a variety of demographic measures. The CVLT-3 includes both standard and alternate forms, one of which will be administered at baseline (V1) and the other will be administered at 24 weeks (V7).

Weschler Adult Intelligence Scale (WAIS)-IV is a measure of cognitive ability for which normative data is available. We will measure working memory using the Digit Span Task. It will be administered at baseline (V1) and 24 weeks (V7).

DSM-5 Cannabis Use Disorder Checklist [47] will evaluate for symptoms of CUD. It will be administered at screening, weeks 0, 12, and 24, and 52-week call.

Timeline follow-back (TLFB) [48] will assess opioids, cannabis, alcohol, nicotine, and other illicit substance use and will be completed at all screening and all study visits.

Alcohol Use Disorder Identification Test (AUDIT) [49] will assess harmful drinking will be administered at screening.

Fagerstrom Test for Nicotine Dependence (FTND) [50] will assess for nicotine dependence in smokers will be administered at screening.

The DSM-5 Opiate Use Disorder Checklist [47] will evaluate for diagnosis and symptoms of OUD will be administered at screening, all study visits, and 52-week call.

The Current Opioid Misuse Measure (COMM) [51] is a brief patient self-assessment that assesses aberrant behaviors associated with misuse of opioid medications will be administered at each study visit

The Prescribed Opioid Difficulties Scale (PODS) [52] will assess common difficulties that patients ascribe to chronic opioid therapy, such as opioid control concerns and psychosocial problems will be administered at each study visit

The Clinical Opioid Withdrawal Scale (COWS) [53] will assess opioid withdrawal symptoms and will be administered at each study visit

The Short Opiate Withdrawal Scale (SOWS) will assess self-reported opioid withdrawal symptoms and will be administered at each study visit.

The Pain Self-Efficacy Questionnaire [54] will be collected at all study visits.

The Pain Catastrophizing Scale (PCS) [55] will be collected at all study visits.

Weschler Test of Adult Reading (WTAR) is a measure to predict full-scale IQ with a range of 0-40.

Monetary Choice Questionnaire *(MCQ* [57]*):* The MCQ presents participants with 27 questions, each of which asks them to choose between smaller, immediate rewards, and larger, delayed rewards. Participants' pattern of answers are able to provide an estimate of their delay discounting rate.

Short UPPS-P Impulsive Behavior Scale[58]*:* The 20-item Short UPPS-P assesses five components of impulsivity, including sensation seeking, lack of premeditation, lack of perseverance, negative urgency, and positive urgency. Scores on many of these factors have been shown to relate to risky behaviors.

Beck Anxiety Inventory (BAI) [59]: The 21-item BAI assess the frequency of anxiety symptoms, including both cognitive and somatic symptoms.

Beck Depression Inventory-II (BDI-II*)* [60]*:* The 21-item BDI-II has shown good reliability and validity for assessing depression in chronic pain patients.

Cannabis Use Disorders Identification Test – Revised (CUDIT-R*)*[61]*:* The CUDIT-R is an 8-item questionnaire that screens for problematic cannabis use in the past six months. It assesses problems related to cannabis use, dependence, and use frequency. The scale ranges from 0 – 32; a score of 13 or higher is indicative of possible cannabis use disorder.

Electronic Cigarette Dependence Index (ECDI*)*[62]*:* The 10-item ECDI assesses dependence on electronic cigarettes. The scale ranges from 0 – 20, with scores 13 and higher indicating high dependence.

ADHD Self-Report Scale (ASRS*)*[63]*:* The 6-item screener scale of the ASRS will be used to assess participants' ADHD symptoms, including both inattentive symptoms and hyperactive-impulsive symptoms, during the past 6 months.

Concise Health Risk Tracking Self-Report form (CHRT-SR)[64]: The 12-item CHRT-SR assesses active suicidal ideation and behavior, perceived lack of social support, and hopelessness. The scale ranges from 0 – 48, with a higher score indicating greater suicidal thoughts and propensity.

Pittsburgh Sleep Quality Index (PSQI*)*[65]*:* The PSQI is a 19-item questionnaire that assesses sleep quality and patterns during the previous month. The scale ranges from 0 - 21, with a higher score indicating less healthy sleep quality.

Social Provisions Scale – 10 (SPS-10*)*[66]*:* The 10-item SPS-10 assesses social support. It measures six social needs, including guidance, reliable alliance, reassurance of worth, attachment, and social integration. The scale ranges from 10 – 40, with a higher score indicating greater social support.

Demographics: Demographic information, including age, sex, gender, sexual orientation, education level, income, race, height, language, employment status, marital status, and residence, as well as information about the participant's caregivers during childhood, will be collected.

Family history*:* The family history subsection of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) [67] will be used to assess family history of psychiatric treatment, including treatment for depression, mania, anxiety, ADHD, schizophrenia, and substance use, as well as history of

suicide.

Distress Tolerance Scale (DTS) will assess perceived capacity to endure distress.

Snaith Hamilton Pleasure Scale (SHAPS) will assess anhedonia and ability to experience pleasure.

Mini International Neuropsychiatric Interview (MINI) [68]*:* The MINI 7.0.2 is a structured diagnostic interview used to assess DSM-5 psychiatric disorders. It will be administered by trained study staff.

The Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD) will be used for diagnosis of lifetime personality disorders at screening.

Peters Delusion Inventory Test (PDI) [69] is a 21-item measure that will assess delusions as well as distress, preoccupation, and conviction.

Medical History: We will assess medical history at screening visit to help determine study eligibility.

Concomitant Medications. We will assess changes to dose, frequency, and use of all concomitant medications at screening and all study visits.

Pregnancy test. Urine will be collected at screening for a pregnancy test.

Adverse events. Adverse events from cannabis (e.g., paranoia, anxiety), fatal or non-fatal overdose events, along with all other AEs (accidents, falls) will be assessed at all study visits.

Readiness Ruler: We will assess stage of change and motivation to reduce opioid dose at all study visits.

PEG (Pain, Enjoyment, General Activity) Scale [70]: The PEG will be used to assess pain intensity and interference. The scale ranges from 0-30, with a lower score indicating lesser pain intensity and interference.

Brief Trauma Questionnaire (BTQ) [71]: The BTQ assesses 10 traumatic events: (1) combat, (2) serious car accident, (3) major natural or technological disaster, (4) life-threatening illness, (5) physical punishment as child, (6) physical assault, (7) unwanted sexual contact, (8) other situation in which respondent was seriously injured or feared being seriously injured or killed, (9) violent death of close friend or family member, and (10) witnessing a situation in which someone was seriously injured or killed or in which respondent feared someone might be seriously injured or killed.

Early Termination

Participants will be terminated from this study if there are any significant safety concerns (e.g., actively suicidal), failure to comply with study procedures, or if the opinion of the principal investigator, can no longer safely participate.

Study compensation

Participants will be paid by check up to $1130 for completing all study procedures. Remuneration will be $20 for the screening visit, $40 for each of 7 study visits, $30 for the follow up phone call, up to $540 for attending the POTS sessions at $20 per session, and up to $260 for daily diary completion from pre-baseline through Week 24, at up to $10 per week (e.g., $1 for each day, and a $3 bonus for completing 7 out of 7 days to incentivize for completeness). You will also be paid up to $5 per study visit for travel costs. Participants will also receive parking validation for parking at MGH garages during study visit.

Week#	visit	
-2	Screening	$20
0	Baseline	$40
4	In person/zoom	$40
8	In person/zoom	$40
12	In person/zoom	$40
16	In person/zoom	$40
20	In person/zoom	$40
24	In person/zoom	$40
52	Phone call	$30
	Dosing Diaries (28 weeks x $10/week)	$280
	POTS sessions (26 sessions x $20/session	$520
Total		$1130

VI. BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected for the study (e.g., data collection sheets).
b. Study endpoints.
c. Statistical methods.
d. Power analysis (e.g., sample size, evaluable subjects, etc.).

Statistical Design and Power:

Aim 1: co-primary outcomes:

1A. Change in PEG scores, from pre-baseline (a 2-week period before the start of MM in the active group) to 24 weeks after initiating MM. The primary outcome for the analysis of the daily PEG scores will be the treatment (MM+POTS vs. WL+POTS) by time. This interaction describes the effect of treatment on reducing pain measured throughout the study. We will estimate this contrast using a longitudinal mixed effects model in order to (A) incorporate covariates as controls, (B) accommodate missing data, and (C) examine trajectories in pain reduction. The preliminary model we propose is as follows: (1) We will test whether the MM+POTS group will show a significant difference in PEG scores from pre-baseline to 24 week time point following the start of MM relative to the WL+POTS group. (2) Fixed effects will incorporate covariates (age, biological sex, type of neuropathic pain, symptoms of OUD, etc.) as additional controls. (3) Month-to-month variation will be handled both by fixed and random effects with an unstructured variance covariance matrix. (4) If necessary, day-to-day variation in PEG scores will be handled by an auto-regressive error term. Changes will be deemed significant for $p < 0.025$, since we will have two primary outcomes. Secondary analyses will estimate (A) whether there is improvement over time using a linear contrast, or (B) whether the effect is immediate and constant.

1B. Change in total opioid dose, in mean daily morphine milligram equivalents (MME), from baseline to 24 weeks, in those assigned to MM +POTS versus WL+POTS. Daily recorded numeric measures from the smartphone app of opioid dose and pain will be analyzed via longitudinal mixed effects models. A conservative Bonferroni-correction will be applied due to comparisons based on two different

outcomes. The analysis of **opioid dose** will be similar to the method proposed in 1A and will use a statistical model incorporating components (1), (2), and (3). However, we expect there will be little variation in daily dose as patients are not usually dosed as needed (PRN). Therefore, we will use the average dose per month, rather than the daily reported dose (However, if substantial variation in daily dose is observed, we can re-incorporate component (4) as needed).

With these two outcomes, a combination of clinical outcomes is possible (see Table 2), which will indicate whether MM is helpful (e.g., decreases opioid doses and/or pain), MM is harmful (e.g., increases opioid dose and/or pain), or that MM has no effect on opioid dose or pain (or increases one outcome and decreases another). In all but particularly the third scenario, costs/benefits to individual patient, including the primary outcomes together with secondary/exploratory outcomes of effect of MM can be evaluated in a cost/benefit consideration of using MM based on the priorities of the individual patient.

Aim 2 Secondary outcomes:

Outcomes will consist of measures collected at each study visit: those for quality of life, pain interference, and depression and anxiety symptoms. These variables will be analyzed with a multivariate multiple regression model (allowing correlations between outcomes to be estimated). Primary predictors will consist of condition (MM+POTS vs. WL+POTS) and time point. Relevant subject-level numeric covariates (i.e. THC/CBD metabolite levels) and categorical factors (e.g. sex, neuropathic pain type) crossed with condition and possibly interacting with time will be included in the analysis. Covariates such as baseline cannabis use, psychiatric diagnosis, and age will be of interest.

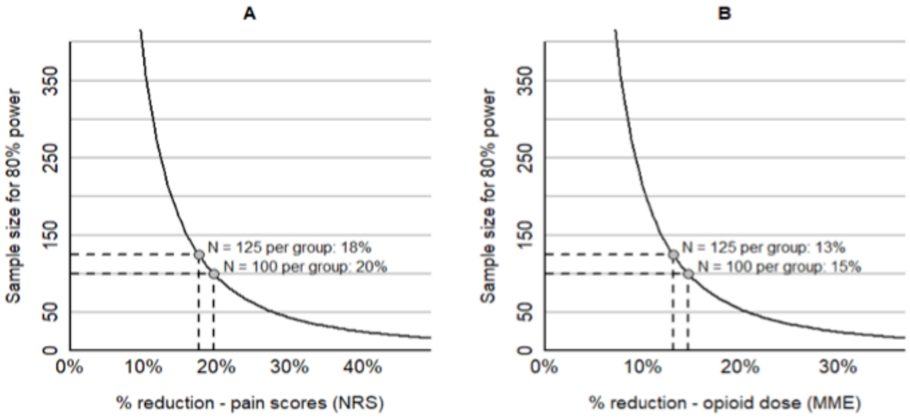
To assess cognitive performance, models will be the same as described above, except that the dependent variable will be change in scores on the cognitive tests (CVLT-III, CPT-3, WAIS-IV). We will co-vary for effects described above, as well as individual differences in baseline cognitive scores, and slope, allowing for individual differences in the rate of change of cognitive scores across assessments.

Aim 3 Assessments at 24 weeks and 1 year in the MM+POTS group:

The incidence of CUD will be estimated from data on the MM+POTS group. We are also interested in determining whether we can find risk factors for CUD in this group. In order to increase power, we will use symptom count as the dependent variable and age, biological sex, and psychiatric diagnoses at baseline as independent variables. This will be analyzed using a binary regression on each symptom with a random effect for each patient.

Power analyses:

Power analyses were conducted looking at the ability to detect our primary contrast of Interest, percent reduction from baseline to the final study time point, between MM+POTS and WL+POTS for the two outcomes, (A) PEG scores and (B) opioid dose. While final analyses will rely on longitudinal mixed effects models, because the key contrast of interest is a pre-post test, power can be approximated via standard methods for independent samples t-tests. Fig 1 shows the sample sizes required to detect different degrees of percent reduction in (A) PEG scores, and (B) opioid dose. Estimates of power for change in pain scores were based on daily diary app data collected during 3 months for 46 participants in our ongoing MM study (See Preliminary Data). Estimates of power for change in opioid doses were based on database information from MGH providers in 2019 detailing opioid prescriptions for 145 chronic pain patients. Points denote the minimum detectable percent reduction for the proposed sample size of 125 subjects per group (250 total), and a worse-case scenario of only 100 subjects per group (20% attrition) by the end of the study. As seen in the figure, even with only 100 subjects per group, we would still have 80% power to detect a reduction of 20% in pain scores and 15% in opioid dose for MM+POTS above and beyond that seen for WL+POTS.



Hypothesis-Generating Analyses: Using the models above, we will conduct planned subgroup analyses in participants with (a) high CBD levels (Cannabidiol glucuronide levels >100), (b) high THC levels (THC-COOH levels >100) and (c) high CBD/THC ratios (1:1 or greater) to assess for a dose response signal with CBD, high CBD/THC ratios and high THC levels. We are likely not powered to detect effects in these small non-randomized groups, however, this data will be valuable for hypothesis-generation in future trials to test specific cannabinoids for pharmacologic effects.

Missing Data:

Our use of a daily survey with payment, as described in the Approach, will reduce the incidence of missing data. To produce unbiased estimates of effects in the presence of missing data, we will use likelihood based mixed models as recommended by Institute of Medicine Guidelines. We understand that there may be some contamination between groups (e.g., some participants in the WL+POTS group may use MM, and some participants in the MM+POTS group may decide not to use MM or may discontinue MM early in the trial). As this is a pragmatic trial, our primary analysis will be an intent-to-treat analysis, in which participants will be analyzed according to their randomization group (MM+POTS vs WL+POTS). This intent-to-treat analysis will be representative of real-world, ecologically valid outcomes, in which a clinician would recommend MM to a patient, and then the patient would come to a decision about whether MM was helpful and its benefits outweighed its adverse effects, and act accordingly. Therefore, this type of analysis, designed for pragmatic trials such as this, will help inform real-world clinical decision-making. However, we do acknowledge that this intent-to-treat analysis cannot answer the question of whether MM has a biological effect on pain and/or opioid use. Therefore, we will also conduct an as-treated analysis, in which we will examine MM without regard to treatment group assignment, by examining those who used MM regularly (weekly or more) vs those who did not use (verified by negative urine screens and no self-reported use). The urine analysis will also provide some information on the different cannabis metabolites and we will try to determine whether there is a differential effect of different constituents.

VII. RISKS AND DISCOMFORTS

Potential risks in the study are considered minimal and include:

1. **Discomfort related to completing questionnaires** about sensitive information such as psychiatric health and illicit substance use: any distress will be minimized by assuring participants that they can refuse to answer any question that they do not feel comfortable addressing and that they may withdraw from the study at any time without penalty. During this clinical trial, we will notify officials, as mandated by law, if a participant reports intention to harm him/herself or others, or reports child abuse or abuse of an elder. In the event a participant were to report a need or interest in treatment for substance dependence, psychiatric disorder, or distress, an appropriate referral to resources will be provided. If there are any concerns about a subject in need of clinical attention, the site PI will be made aware of the

issue immediately and determine appropriate steps. The PI and/or medically trained co-investigators will assess the needs of the subject and offer the subject either prompt treatment or medical referral, whichever is appropriate for the situation. There is a licensed clinician at each site 40 hours per week.

2. **Breach of confidentiality and/or privacy**: Protecting the confidentiality and integrity of our research participants is a top priority for this and all MGH-based research projects. Any breach is unlikely because all information will be identified with a numeric code only and stored on password-protected servers. Only study staff will have access to this database. All staff will be fully trained in relevant ethical principles and procedures, including confidentiality. All assessment and treatment procedures will be closely supervised by the PI. Electronic data capture will also be safeguarded. Data will be collected using REDCap (Research Electronic Data Capture) tools hosted by MGB HealthCare. REDCap is a secure, web-based application designed to support data capture for research studies, and which is fully compliant with HIPAA-Security guidelines. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from MGB HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. Self-report questionnaires will be administered via REDCap on MGB encrypted tablets, minimizing the risk of confidentiality breaches. Only authorized MGH project members will be allowed access to these tablets. Both REDCap and REDCap Survey systems provide secure, HIPAA compliant, web-based applications.

Confidentiality will be maintained by numerically coding all data, by removing identifying information, and by keeping all data in locked file drawers in locked offices. Any data files in electronic format will be housed in our network server at the Center for Addiction Medicine at MGH and will be password protected in encrypted devices so that only authorized project personnel have access to them. Individually identifiable information about human subjects will be accessible only to research staff. All study staff will be trained in protection of privacy of research participants and will be CITI certified. Information about study participants will not leave the institution in any form that would identify individual subjects. Data will be transmitted with subjects identified only by code.

Limits of Confidentiality on Clinical Information (Emergency Protocol): While we are committed to maintaining confidentiality to the extent to which we are able, confidentiality is limited when there is a deemed imminent risk to oneself or others or reports of child and elder abuse. Study staff will inform participants during the consent process that in emergency situations (in which an individual is at immediate risk for harm) we will release information about the participant. Specifically, if a participant tells any member of study staff that he/she has intent and/or a plan to cause harm to self or others, study staff will start the Center Emergency protocol that includes a psychiatric evaluation by a licensed mental health professional and even calling 911. If the participant says that he/she has recurrent thoughts about harming him/herself or someone else but does not have intent or plan to do so, study staff will ask participant permission to notify appropriate medical or counseling personnel, including the guidance counselor or therapist. If study staff learns about mood concerns or problematic substance use, study staff will provide the participant with referral resources for follow-up consultation and care. The PI has prepared a comprehensive list of local and national resources for this purpose.

3. **Discomfort/adverse events with opioids:** While it is expected that opioid withdrawal symptoms will be extremely rare, we will assess opioid withdrawal symptoms in all participants throughout the study. At in person visits, opioid withdrawal will be assessed. Study participants will also rate their craving for opioids in the past week on the Short Opiate Withdrawal Scale (SOWS), a 10-item questionnaire developed to evaluate opioid withdrawal symptom severity. If there are any concerns about a subject in need of clinical attention, the MPIs and study physicians will be made aware of the issue immediately and will determine appropriate steps. The PIs and medically trained co-investigators will assess the needs of the subject and offer the subject either prompt treatment or medical referral, whichever is appropriate for the situation. Further, we will collect extensive safety and tolerability data, including opioid withdrawal symptoms, that will be reviewed quarterly by the DSMB and revisions to procedures will be instituted if indicated.

While opioid overdose is not expected, as participants will not be increasing their opioid dose as part of this study, the study team has the following plan in place to manage potential opioid overdose. We expect

that all participants will have naloxone since they are on COT. During the first POTS group session, naloxone will be discussed, and group leaders will recommend that all participants obtain a naloxone kit. In the state of MA, the Department of Public Health has issued a statewide standing order that allows retail pharmacies to dispense naloxone without a prescription. If participants decline to obtain naloxone, we will schedule a one-on-one meeting to explore their concerns and explain the benefits of having a naloxone kit.

4. **Discomfort/adverse events with medical cannabis (MM) use**: Cannabis is associated with reversible effects on appetite, mood, cognition, memory, and perception. At low to moderate doses, THC can produce behavioral intoxication and physiological changes (feeling intoxicated, high, euphoric, dizzy, giddy, tired and lightheaded; increased heart rate, and slowed reaction time). Participants may experience changes in behavioral, symptoms, or cognition that they find disturbing or troubling if they do escalate cannabis use. Some participants will experience adverse events including increased anxiety, paranoia, sleeping difficulties, or temporary psychosis. Some studies have found associations between cannabis use and suicidal thoughts. Some participants may develop cannabis use disorders as a result of using MM. Though study participants will choose what type and how much cannabis to use and when, we will recommend that participants do not use certain types of marijuana products (e.g., waxes, shatter) that are more likely to lead to dependence. Long-term effects of MM are still unknown. Other potential adverse events from using MM are risk of psychosis and worsening depression. Vaping has been linked to cases of serious lung injury, some resulting in death. While the exact cause is still not confirmed, the CDC recommends that people not use vapes. Symptoms of vaping-related lung injury include rapid onset of coughing, breathing difficulties, weight loss, nausea and vomiting, and diarrhea. These will all be important outcome measures of this study, which will be carefully measured and assessed at each study visit. Subjects will be encouraged to report adverse events at any time by calling study staff. Study staff who will be interacting with subjects are clinically trained and able to assess need for medical or professional intervention, and will ensure prompt treatment or medical referral for any participant requiring medical or professional intervention during the study. If there are any concerns about a subject in need of clinical attention, the MPIs and Site PIs will be made aware of the issue immediately to determine appropriate steps. The MPIs and medically trained co-investigators will assess the needs of the subject and offer the subject either prompt treatment or medical referral, whichever is appropriate for the situation. There is a licensed clinician at each site 40 hours per week, and other MGH resources can be used as necessary. Further, MM-related AEs will be reviewed quarterly by the DSMB and revisions to procedures will be instituted if indicated.

Serious adverse events are not expected. Any SAEs that do occur will be reported by telephone or email by the principal investigator to the Partners IRB according to current PHRC Adverse Event Reporting Policy (version dated: March 13, 2007). All adverse events (if not serious) will be reported in writing to the Partner's Human Research Committee at a yearly Continuing Review.

5. **Legal/Social Risk from using MM**: There are few legal risks to the participants associated with these paradigms. Cannabis use is for medical and recreational use is legal in Massachusetts, thus there is no legal risk to self-report of regular cannabis use. Socially, some subjects may be embarrassed if others found out that they were using MM. Therefore, we will protect privacy and confidentiality of all participants.

Confidentiality of Drug Tests: The results of the qualitative and quantitative drug testing will be confidential. When submitting requisition forms to the Pharmacy and Therapeutics Committee at the University of Colorado School of Medicine, only the assigned identifying code will be included, there will be no information on the forms that non-study staff could associate with a specific participant. The only individuals who will have knowledge of the results of these tests are research staff directly working on the project. Information will be stored in a secure computer database that uses participant codes (rather than names) as identifiers.

6. **Randomization in clinical trials**: Participants will be assigned to an intervention by chance. The intervention to which a participant is assigned may prove to be less effective than the alternate intervention.

VIII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals:

Participants may find that POTS and medical cannabis are helpful for opioid tapering, and may experience associated benefits. Participants may also find that talking about cannabis and opioid use increases their awareness of any issues related to drug use. Any participant who asks about treatment will be provided information regarding local drug treatment programs. Participants may experience pain reduction or reduce their opioid dose. Further, millions of individuals have CNCP that is very often debilitating and complex, and clinicians have few strategies to meet the complex medical needs of this patient group. This study could potentially benefit other patients with CNCP. Thus, the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

b. Potential benefits to society:

MM use has now been sanctioned by several states as a treatment for both chronic pain and for OUD with very little evidence of effectiveness for either indication. Thus, the proposed study will answer a timely and critically important public health controversy over whether MM use is beneficial or harmful in this population, information that will be critically important to patients, healthcare providers, and policymakers. The proposed project will fill a critical gap in our knowledge, at a critical time when cannabis is being legalized for 'medical' use with little known about effects of MM on target symptoms such as pain, addictions, or neurocognition.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data:

Data Management: All data management will be conducted in the offices of the PI at the MGH Center for Addiction Medicine (CAM) in Boston. Standard REDCap data collection forms for all proposed clinical rating scales will be used. Tablets with HIPAA compliant REDCap capability will be used to capture raw data from clinical rating scales entered by participants and study staff. A study database will be designed by the PI and the data manager and maintained by the PI, the data manager and the research coordinators. The data manager will review the data weekly. Access to the database is restricted by password. The database will be protected by nightly backup on MGH servers. All data will be stored safely for at least 5 years after study completion.

b. Safety monitoring: DSMB

An independent Data and Safety Monitoring Board (DSMB) will be appointed for this study, to assess safety of this clinical trial by determining whether there is an unacceptable level of risk due to MM and whether an increased number of adverse events occur in the MM+POTS group compared with the WLC+POTS group.

The DSMB will be made up of at least one psychiatrist, one statistician, and one addiction neuroscientist. The psychiatrist will serve as the Chair of the DSMB**.** Each member of the DSMB will not otherwise be associated with the trial.

The Study Biostatistical team will provide the reports to the DSMB. Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons. Range of Safety Reporting to the DSMB: It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but other data that may reflect differences in safety between treatment groups. This includes treatment retention rates, reasons for drop-out, and clinical outcome.

Safety data will be informally reviewed every 3 months by the study team, and formally reviewed by the Data and Safety Monitoring Board when 25%, 50%, 75%, and 100% of the sample have been enrolled. When half the sample has been enrolled, a blind analysis of efficacy and safety data will be conducted by the Data and Safety Monitoring Board if deemed appropriate by the DSMB chair, NIDA, or the Project Officer. Criteria for trial stopping rules will be reviewed with the DSMB and submitted to

the Project Officer. A DSMB Report written by the chair and approved by all members will be issued to the NIDA Project Officer after every DSMB meeting.

c. Outcomes monitoring

A DSMB Report written by the chair and approved by all members will be issued to the IRB and the NIDA Project Officer annually. The report will include, but may not be limited to, a synopsis of the trials, their progress to date, characteristics of participants enrolled, retention and disposition of study participants, quality assurance issues, regulatory issues, and reports of AEs and SAEs.

Criteria for trial stopping rules:

When half the sample has been enrolled, a blind analysis of efficacy and safety data will be conducted. Criteria for trial stopping rules will be reviewed with the DSMB.

d. Adverse event reporting guidelines

Study staff, including co-investigators, research coordinators, and data managers, will meet weekly with the PIs and the Project Director during a weekly project management meeting to review study progress, including any adverse events.

All adverse events volunteered, observed, or solicited will be recorded in the AE CRF from the time the subject signs the informed consent up to and including the last visit. The PI will meet weekly with all study investigators to review the details of data acquisition and analysis as well as any minor problems. AEs will be assessed for each subject at every visit. All adverse events will be recorded and will include the dates of occurrence; severity; assessment of relationship to study drug; countermeasure(s); specific drug therapy used in countermeasure; and outcome. Adverse events will be reviewed by the PI who will complete an adverse event report form and submit this to the IRB within the required time frame in accordance with the IRB guidelines.

Reporting Adverse Events (AEs): The principal investigator will report all adverse events experienced by the study subjects in accordance with HRC (Human Research Committee) guidelines to the Institutional Review board. Adverse events will also be reported by the principal investigator to the funding agency and to the FDA in accordance with IND regulations.

In case of serious adverse events (SAE's), the principal investigator will report them within 24-hours by telephone, fax or email according to HRC guidelines, followed by a written report within 5 business days. An annual report will be submitted to the HRC of the progress of the trial. This will include individual study information and information on safety reports from the previous year.

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