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# Randomised, pragmatic, waitlist controlled trial of cannabis added to prescription opioid support on opioid dose reduction and pain in adults with chronic non-cancer pain: study protocol

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## ABSTRACT

**Introduction** Chronic, non-cancer pain impacts approximately 50 million adults in the USA (20%), approximately 25% of whom receive chronic prescription opioids for pain despite limited empirical efficacy data and strong dose-related risk for opioid use disorder and opioid overdose. Also despite lack of efficacy data, there are many reports of people using cannabis products to manage chronic pain and replace or reduce chronic opioids. Here we describe the protocol for a randomised trial of the effect of cannabis, when added to a behavioural pain management and prescription opioid taper support programme, on opioid utilisation, pain intensity and pain interference.

**Methods** This is a pragmatic, single-blind, randomised, wait-list controlled trial that aims to enrol 250 adults taking prescription opioids at stable doses of ≥25 morphine milligram equivalents per day for chronic non-cancer pain who express interest in using cannabis to reduce their pain, their opioid dose or both. All participants will be offered a weekly, 24-session Prescription Opioid Taper Support group behavioural pain management intervention. Participants will be randomly assigned in 1:1 ratio to use cannabis products, primarily from commercial cannabis dispensaries or to abstain from cannabis use for 6 months. Coprimary outcomes are change in prescription monitoring programme-verified opioid dose and change in Pain, Enjoyment, General Activity scale scores. Secondary outcomes include quality of life, depression, anxiety, self-reported opioid dose and opioid and cannabis use disorder symptoms. All other outcomes will be exploratory. We will record adverse events.

**Ethics and dissemination** This study has ethical approval by the Massachusetts General Brigham Institutional Review Board (#2021P000871). Results will be published in peer-reviewed journals and presented at national conferences.

**Trial registration number** NCT04827992.

## STRENGTHS AND LIMITATIONS OF THE STUDY

⇒ This randomised, pragmatic trial in adults on chronic opioids for non-cancer pain will test whether cannabis use is associated with reduced opioid dose and reduced pain ratings when added to a behavioural pain management intervention.
⇒ We aim to enrol 250 participants across three sites, which will provide sufficient power to analyse the two primary outcomes, change in prescription monitoring programme-verified opioid dose and Pain, Enjoyment and General Activity score.
⇒ This pragmatic trial makes use of the cannabis distribution system being put into place in many US states and, as such, a limitation of this study is that it cannot include a placebo or control for the type or amount of cannabis used by participants.

## INTRODUCTION

Approximately 50 million adults in the USA suffer from chronic, non-cancer pain (CNCP),[1] a debilitating medical condition that is challenging to manage. Though nearly 25% of those with CNCP are treated with chronic opioid therapy (COT),[2] the evidence to support the long-term effectiveness of opioid analgesics for pain and functional status is limited.[3] In addition, high dose COT increases the risk for opioid use disorder (OUD) and subsequent opioid overdose death.[4–9] The proposed CDC Clinical Practice Guidelines for Prescribing Opioids-2022[10] recommends several strategies to mitigate risks of opioid use for chronic pain. These include the following: (1) initiating opioid therapy only if expected benefits to pain management and functioning outweigh risks, (2) utilising non-opioid and non-pharmacologic approaches for pain management, (3) prescribing the lowest dosage to achieve expected effects and (4) working collaboratively with patients to taper to lower dosages if risks outweigh benefits of continued use.[10] Available evidence indicates that COT dose reduction generally improves

pain, function and quality of life for individuals with CNCP.[11] However, since optimal strategies for helping individuals reduce their opioid dose in real-world settings are largely unknown,[12] there are concerns that the risk for overdose increases during tapering due to rapid discontinuation and variability in dosing.[13–15]

Cannabis and cannabinoids have been explored as potential treatments for chronic pain, and chronic pain is the most common reason individuals give for seeking state-issued medical cannabis cards.[16] However, there is inconclusive evidence regarding the effectiveness of cannabis in facilitating analgesia.[17] A Cochrane review of randomised controlled trials (RCTs) of cannabinoids for pain included studies of nabilone (FDA approved synthetic THC, two studies), dronabinol (plant-derived THC, two studies), sativex (nabiximols in the USA, an oromucosal spray with a 1:1 ratio of plant-derived THC and cannabidiol (CBD), 10 studies) and combusted herbal cannabis (two studies) and concluded that there was a lack of evidence that any cannabis-derived product was effective for any form of chronic pain.[18] A review by the Department of Veterans Affairs[19] similarly concluded that there was insufficient evidence to support efficacy of cannabis products for chronic pain. Though, it is worth noting they reported that low-quality evidence suggested cannabis may alleviate neuropathic pain for some patients. A recent RCT found no effect of commercial cannabis products obtained with medical marijuana cards on self-rated pain scores.[20] Yet, a 2017 report from the National Academies of Sciences, Engineering and Medicine[21] reported "conclusive or substantial evidence" that cannabis is effective in treating chronic pain. Thus, there are contradictions in the literature surrounding the effectiveness of cannabis products for managing pain.

Despite the lack of sufficient evidence, cannabis began to be promoted as a substitute for opioids following a widely publicised study reporting that states with legal medical cannabis had lower-than-expected opioid overdose mortality rates from 1999 to 2010.[22] Despite a reanalysis of state-level data through 2017 that showed the opposite trend[23] and no studies demonstrating efficacy, cannabis has been approved by many states as a 'treatment' for OUD.[24] Although a recent systematic review suggests that cannabis used in combination with opioids to treat CNCP may reduce opioid dose,[25] to date, there are no published reports of RCTs investigating the effectiveness of cannabis for reducing opioid utilisation. Still, many patients self report using cannabis as an alternative to to pharmaceutical prescriptions, including opioids and adjuvant therapies.[26]

Behavioural interventions are associated with sustained improvements in functioning for those with chronic pain,[27] particularly among those with co-occurring mental health diagnoses.[28] Patients with CNCP and comorbid mental health diagnoses are more likely to be prescribed opioids, be prescribed a higher dose and to report chronic opioid use, compared with those with CNCP without mental health conditions.[29–33] The current study utilises a behavioural intervention, based on the Prescription Opioid Taper Support (POTS) programme,[34] to help participants develop pain self-management skills and promote an individualised, voluntary opioid taper with a goal of a 10% reduction from the baseline dose every 4 weeks. Drawing on several therapeutic modalities, including cognitive behavioural therapy and motivational interviewing, this intervention promotes a strong therapeutic relationship and encourages participant autonomy in problem-solving challenges associated with chronic pain.[35 36]

### Objectives

The goal of this study is to provide controlled trial data about the potential benefits and unintended consequences of using cannabis, primarily from commercial cannabis dispensaries, to treat CNCP; we hope that these findings can help patients and providers make more informed treatment decisions. The primary objective of this study is to evaluate whether cannabis (CB), when added to the 24-week POTS programme, reduces opioid dose and/or improves pain intensity and interference in adults on COT for CNCP from baseline to 24 weeks, more so than those assigned to a waitlist (WL) conditon in which they agree to wait 6 months to use cannabis, but receive the POTS intervention (WL+POTS). Prescription Monitoring Programme (PMP)-verified opioid dose and Pain, Enjoyment and General Acitivity (PEG)[37] score are our coprimary outcomes.

The secondary objectives are to evaluate whether participants assigned to CB+POTS, compared with those assigned to WL+POTS, have improved quality of life, depression, anxiety and reduced self-report opioid dose from baseline to 24 weeks. This study will evaluate changes in the number of OUD symptoms, as well as whether those assigned to CB+POTS develop symptoms of cannabis use disorder (CUD) over the 24-week intervention and at 12 months.

## METHODS AND ANALYSIS

The full protocol is included as supplementary information (online supplemental file 1).

### Study design

A randomised, pragmatic, single-blind controlled trial.

### Study population

Adults ages 18–75 years old at three academic hospitals in the Northeastern USA (Massachusetts General Hospital, Cambridge Health Alliance, Maine Medical Centre) with CNCP on stable prescription opioid doses of ≥25 morphine milligram equivalents (MME)/day for at least 90 days who plan to use cannabis to control pain and/or reduce opioid dose will be invited to participate. Participants will be recruited through physician referrals, clinical programmes associated with the healthcare systems and community advertising. Importantly, to be

**Box 1 Inclusion criteria**

1. Men and women aged 18–75, inclusive.
2. Endorsing>6 months of chronic, non-cancer pain.
3. On stable prescription opioid doses of ≥25 morphine milligram equivalents/day for >90 days, verified by the prescription monitoring programme.
4. Either no prior use or current light cannabis use (weekly or less in the past 12 months, less than 10 times in the past 90 days).
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 enrolment and agree to use effective contraception: abstinence; hormonal contraception; intrauterine device, sterilisation or double barrier contraception, during the study.

**Box 2 Exclusion criteria**

1. Current cannabis use (including ingested/inhaled cannabidiol products) of greater than weekly on average in the past 12 months, assessed via self-report (no more than 10 times in the past 90 days).
2. Current cannabis use disorder; moderate to severe substance use disorder for any substance (eg, alcohol, cocaine, stimulant) by structured interview, EXCEPT nicotine and opioids (opioid use disorder).
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 (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), gabapentin, non-steroidal anti-inflammatory drugs) in the past 4 weeks, verified by electronic health record.
6. Concomitant medications will be discussed at each study visit, and any medications that may interact with cannabinoids (eg, warfarin) will be discussed with a study clinician prior to enrolment or continued participation.
7. Actively suicidal and/or suicide attempt or psychiatric hospitalisation in past year, or current suicidal ideation with specific plan or intent.
8. History of intellectual disability (eg, Down's syndrome) or other severe developmental disorder or IQ<70.
9. Current diagnosis of delirium, dementia, amnestic or other cognitive disorder; current diagnosis of bipolar II disorder; lifetime diagnosis of a clinically significant personality disorder (eg, borderline, antisocial, paranoid, schizoid, schizotypal, histrionic personality disorders); lifetime diagnosis of bipolar I, 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.

eligible, participants must be willing to abstain from any cannabis use during the intervention and to wait 24 weeks before using cannabis if they are randomised to the WL+POTS group. A full list of inclusion criteria can be found in box 1. Exclusion criteria include current regular cannabis use (>weekly) in the past 12 months, use of non-prescribed opioids and uncontrolled major medical illness. Current moderate to severe substance use disorders, with the exception of tobacco and OUDs, are also exclusionary. A full list of exclusion criteria can be found in box 2.

### Participant enrollment

Interested participants will complete a telephone screen for eligibility. All individuals who are potentially eligible based on the phone screen will be scheduled for an enrolment visit where written informed consent will be obtained by a trained member of study staff. The consent form is available as supplemental information (online supplemental file 2). Study physicians or their delegates will use the PMP to document prescriptions for opioids and other medications monitored by the PMP. Additionally, they will use the electronic health record to document concomitant medications to improve the accuracy of self-reported of current medications.

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

### Randomisation and allocation concealment

After the baseline visit, participants will be randomly assigned 1:1 to CB+POTS: WL+POTS in blocks of 3–6 (depending on speed of recruitment). If more patients drop out in the WL+POTS group, participants will be randomised in blocks, 1:2 CB+POTS:WL+POTS to achieve the goal of 100 patients completed in each arm by the end of the trial.[20] Block randomisation will be done so that groups will be comprised only of participants in the same randomisation group; thus, those assigned to CB+POTS would not be in the same behavioural pain management groups as those assigned to WL+POTS .

Randomisation will be computer generated. Assessments will be conducted by study staff blind to the study intervention. Blinding of participants after group assignment is not possible due to the study design.

### Interventions

Participants will be assigned to either begin cannabis use without delay (CB+POTS), or to a waitlist control (WL+POTS), in which they are incentivised through payments, to wait 24 weeks before beginning to use cannabis. After the 24-week period, those in the WL+POTS group will have the option to begin cannabis use. This is a pragmatic trial in which participants choose their cannabis products, dose and frequency of use, which mimics the certification process for cannabis in

many states (where patients have a broad range of choice in products and dosing) and mimics the use of recreational cannabis outside of any healthcare interactions. All participants will continue other medical care as usual.

All study participants, regardless of randomisation group, will participate in the POTS programme. POTS is a 24-week intervention that teaches behavioural pain self-management strategies and supports a voluntary taper of COT dose. POTS was developed by Turner and Sullivan,[34] and will be modified in this study to (1) allow for implementation in a group format, (2) reorder skill training based on the perceived difficulty of the skills being taught and (3) increase length of the programme from 18 to 24 weeks. There will be two additional sessions in weeks 25–26 to facilitate return of care to the primary care physician. During the five POTS sessions in study weeks 4–20 that coincide with monthly study visits, study clinicians will work with participants to reduce opioid dose in increments of approximately 10% of the baseline opioid dose. POTS sessions will be conducted virtually via teleconference with groups of 3–6 study participants and will last 1 hour. Sessions will be led by a trained clinician and use components of cognitive behavioural therapy, mindfulness and motivational interviewing to help individuals better manage their chronic pain and achieve an opioid

**Table 1** POTS session content

| Session | Content |
|---|---|
| Session 1 (individual) | Individual session to discuss pain and opioid use history, goals for taper |
| Session 2 | Group introductions, relationship building, set expectations for participation, introduce tapering schedules, discuss overdose prevention strategies |
| Session 3 | Psychoeducation: chronic opioid therapy |
| Session 4* | Diaphragmatic breathing |
| Session 5 | Psychoeducation: pain neurobiology and pain gate theory |
| Session 6 | Psychoeducation: pain neurobiology and pain gate theory |
| Session 7 | Relaxation techniques and introduction to seven muscle group progressive muscle relaxation |
| Session 8* | Guided practice of seven-muscle group progressive muscle relaxation |
| Session 9 | Diaphragmatic breathing-guided practice; psychoeducation on importance of sleep |
| Session 10 | Distraction for pain relief |
| Session 11 | Pacing and activity scheduling |
| Session 12* | Counterstimulation |
| Session 13 (individual) | Individual session to discuss opioid taper, experience with behavioural pain self-management techniques, individual challenges |
| Session 14 | Coping with pain flare-ups |
| Session 15 | Brief diaphragmatic breathing; introduction and practice of four-muscle group progressive muscle relaxation with tension |
| Session 16* | Introduction and practice of four-muscle group progressive muscle relaxation without tension and guided practice |
| Session 17 | Developing positive coping thoughts and coping self-statements |
| Session 18 | Psychoeducation: self-compassion |
| Session 19 | Brief body scan |
| Session 20* | Mini-relaxation and incorporation into daily routine |
| Session 21 | Pain beliefs and activity avoidance |
| Session 22 | Setting pleasurable activity goals |
| Session 23 | Psychoeducation: social and emotional factors that influence pain |
| Session 24 | Maintaining gains and dealing with setbacks |
| Session 25 | Group termination, skills review, facilitation of return of care to Primary Care Provider |
| Session 26 (individual) | Individual termination session, facilitate return of care to Primary Care Provider |

*Taper Point.
POTS, Prescription Opioid Taper Support.

dose reduction. POTS session content can be found in table 1.

### Data collection

Participants will complete a daily online survey with questions regarding pain intensity and interference (PEG scale; range, 0–30), cannabis use, opioid use (MME/day) and ratings of sleep quality, mood and general health. Daily survey data will be assessed from 2 weeks pre-baseline to 24 weeks.

Study visits will take place approximately at weeks 0 (baseline), 4, 8, 12, 16, 20 and 24. Data collection at these visits will include self-administered and clinician-administered assessments. Assessments will use standard, validated measures, selected for consistency with the PhenX Toolkit,[38] the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for chronic pain trials[39] and the National Institutes of Health (NIH) Research Standards for Chronic Low Back Pain.[40] A follow-up assessment will also be conducted at 12 months by telephone.

At all study visits, participants will provide a urine sample which will be qualitatively screened for substances, including opioids and cannabinoids, and used to verify that those assigned to WL+POTS are not using cannabis prior to week 24. Urine samples from the CB+POTS group will be sent to the Pharmacy and Therapeutics Committee at the University of Colorado School of Medicine for a quantitative metabolite assay to measure cannabis metabolites.

### Outcomes

The primary outcome is to evaluate whether adults with CNCP on COT assigned to CB+POTS, compared with those assigned to WL+POTS, have (1) greater reduction in PMP-verified opioid dose (MME/day) at 24 weeks compared with baseline, and/or (2) greater improvement in pain intensity and interference (PEG scores) from postbaseline to 24 weeks as assessed by daily diaries (coprimary outcomes).

The secondary outcomes of this study are to evaluate whether participants assigned to CB+POTS, compared with those assigned to WL+POTS, have improved quality of life, depression and anxiety and reduced self-reported opioid dose.

We also plan to evaluate whether those assigned to CB+POTS have a reduced number of OUD symptoms at 24 weeks compared with WL+POTS, as well as if they have developed symptoms of CUD at 24 weeks. See box 3 for a full list of outcome measures.

Box 3 All outcomes will be analysed as mean difference in scores between baseline and 24 weeks, unless otherwise noted.

**Box 3 Outcome measures**

**Primary outcome measures**

- Prescription monitoring programme-verified opioid dose (morphine milligram equivalent; MME) per day.
- Pain intensity and interference (Pain, Enjoyment, General Activity (PEG) Scale[37] summed score).

**Secondary outcome measures**

- Quality of life (Quality of Life, Enjoyment and Satisfaction Questionnaire-Short Form, Q-LES-Q-SF[44]).
- Depressive symptoms (Patient Reported Outcomes Measurement Information System-29, PROMIS-29 Depression subscale[45]).
- Anxiety symptoms (Patient Reported Outcomes Measurement Information System-29, PROMIS-29 Anxiety subscale[45]).
- Opioid use disorder symptoms (DSM-5 Opioid Use Disorder Checklist[46]).
- Cannabis use disorder symptoms (DSM-5 Cannabis Use Disorder Checklist[46]).
- Self-reported opioid dose (MME/day) collected daily via online survey and then averaged over each month at 24 weeks.

**Exploratory outcome measures**

- Opioid misuse (Current Opioid Misuse Measure, COMM[47]).
- Opioid-related problems (Prescribed Opioid Difficulties Scale, PODS[48]).
- Opioid withdrawal symptoms (Clinical Opiate Withdrawal Scale, COWS;[49] Short Opioid Withdrawal Scale, SOWS[50]).
- Opioid use disorder symptoms (DSM-5 Opioid Use Disorder Checklist[46]) at 12 months.
- Cannabis use disorder symptoms (DSM-5 Cannabis Use Disorder Checklist[46]) at 12 months.
- Self-Efficacy (Pain Self-Efficacy Questionnaire, Disorder[51]).
- Pain Catastrophising (Pain Catastrophising Scale, PCS[52]).
- Distress Tolerance (Distress Tolerance Scale, DTS[53]).
- Anhedonia (Snaith-Hamilton Pleasure Scale, SHAPS[54]).
- Delay Discounting (Monetary Choice Questionnaire, MCQ[55]).
- Psychotic Experiences (Peters Delusion Inventory, PDI[56]).
- Suicidal thoughts and behaviours (Concise Health Risk Tracking Scale, CHRT[57]).
- Readiness to change (Readiness Ruler[58]).
- Cognitive function: Verbal (California Verbal Learning Test-Third Edition). [59]
- Cognitive function: working memory (Weschler Adult Intelligence Scale-IV Digit Span Task[60]).

### Withdrawal from the study

All participants will be informed that participation in the research study is voluntary, and they can withdraw and end their participation at any time. Study staff will work to ensure withdrawn participants stop the study safely and will arrange for follow-up care if needed.

### Duration of the trial

It is anticipated that the study will be completed in 4 years (November 2021–March 2025). Primary and secondary outcomes will be accomplished by the end of year 3.

### Confidentiality

Patient confidentiality will be protected according to the regulations set forth by the Mass General Brigham Institutional Review Board (IRB). Participants are informed that all records are kept confidential. Paper records are secured in a locked office, and computer data protected with passwords and file access standards.

### Data management and statistical analysis

Data will be collected prospectively and managed using a REDCap[41 42] database designed by the principal investigators and data manager at MGH. Data will be entered by IRB-approved study staff who are trained in best practices for human subjects research. Daily survey data will be entered directly by participants who will be trained on how to use the application and correctly enter data. The data manager will check data weekly for quality and accuracy.

Baseline patient characteristics by treatment group will be presented as mean (SD), median and count (%), depending on type.

Our coprimary outcomes will be the summed score (ranging from 0 to 30) of the three-item PEG scale, a measure of pain intensity and interference, and total opioid dose in mean daily MME. We will analyse both outcomes using a linear regression model. PEG will be collected daily via self-report through an online survey from baseline to the end of the 24-week period (ie, up to 168 observations per subject), and opioid dose will be verified though the PMP. All postbaseline daily observations for PEG scores will be analysed.

The confirmatory effect of interest for opioid dose will be the treatment (WL+POTS vs CB+POTS) by time (baseline vs week 24) interaction, testing whether there is a significant reduction in opioid dose at week 24 for CB+POTS above and beyond any reduction for WL+POTS. If participants decide to reduce dose at week 24, we will use the reduced dose even if the new dose cannot be immediately implemented (eg, due to delays in refilling prescription) to ensure accurate representation of change.

The confirmatory effect of interest for PEG scores will be a dummy-coded contrast between WL+POTS (the referent, coded as 0) and CB+POTS (coded as 1), testing whether a constant effect of CB exists, averaged over all time points. Additionally, as covariates we will include terms for (a) a quadratic time trend, (b) baseline PEG scores and (c) baseline opioid dose. We assume a conservative additive model, with main effects for the impact of CB and monthly trends, but no treatment by time interaction.

Coefficients and standard errors for the linear model will be obtained using generalised estimating equations.[43] The primary contrast testing for a constant effect of CB above and beyond POTS will be deemed statistically significant for $p<0.025$, thereby adjusting for multiple comparisons given that we have two outcome measures.

We will also conduct sensitivity analyses for each outcome. First, we will examine if the direction and significance of the primary contrast for CB+POTS and WL+POTS is robust to the inclusion of additional covariates that includes a treatment by time interaction. Second, we will examine if the direction and significance of the primary contrast for CB+POTS is robust to our treatment of missing data by fitting the statistical model to the observed data only. Finally, we will conduct an as-treated analysis examining those who used CB regularly (weekly or more) versus those who did not use (verified by negative urine screens and no self-reported use), correcting for "confounding by indication" by weighting data by the inverse probability of being in the CB or non-user group. Additional sensitivity analyses may be required to address unanticipated developments throughout the course of the study.

Examination of PEG scores and opioid dose means that a combination of clinical outcomes is possible (see table 2), which will indicate whether cannabis is helpful, cannabis is harmful or that cannabis has no clear effect on opioid dose/PEG scores. In the third condition, an exploratory analysis will evaluate costs/benefits of cannabis to the individual patient, measured via secondary outcomes, (eg, effect of cannabis on sleep, mood).

Secondary outcomes will consist of measures collected at each monthly study visit (measures of quality of life, depression, anxiety, OUD, CUD and self-reported opioid dose). Secondary outcomes will be analysed using the same statistical model as PEG scores, but with the quadratic time trend defined over the monthly visits.

We will use multiple imputation via chained equations to address missing data for both primary and secondary outcomes. Subjects with fewer than 14 days of daily diary entries will be excluded. For daily PEG scores, for runs of missing data (multiple days in a row with missingness), the first and last entry of the run will be imputed.

### Sample size

While final analyses will rely on linear regressions robust to clustering and heteroscedasticity, because the key contrast of interest is the mean difference between CB+POTS and WL+POTS, power can be approximated via standard methods for independent sample t-tests. The target sample size was 125 subjects per group, or 100 subjects under a worse-case scenario of 20% attrition. A power curve for each outcome was computed, plotting the required sample size for 80% power against the associated minimum detectable percent reduction in the outcome measure.

For PEG scores, power curve estimates were based on preliminary data, 3205 daily pain scores (a component of PEG scores) reported by 46 subjects in our previous cannabis use study[20] over a period of 84 days (roughly 3 months). The mean (6.3) and SD (3.1) for pain scores in the first 2 weeks was used to compute percent reduction. For 125 subjects per group, we would have 80% power to detect a minimum percent reduction of 18% in PEG scores for the CB+POTS group above and beyond that for the WL+POTS group. Even with only 100 subjects per group, we would have 80% power to detect a minimum percent reduction of 20% in PEG scores for the CB+POTS group above and beyond that for the WL+POTS group.

For opioid dose, power curve estimates were based on opioid dose data extracted from 2017 MGH records for the 145 PEG score patients. We used the mean (88) and SD (32) in MME to compute per cent reduction.

Table 2 Clinical significance table

| Decision | PEG scores at 6 months compared with baseline | Opioid dose at 6 months compared with baseline | Meaning |
|---|---|---|---|
| CB is beneficial | CB+POTS < WL+POTS | CB+POTS < WL+POTS | CB reduces PEG score and decreases opioid dose |
| | CB+POTS < WL+POTS | ns | CB reduces PEG score and does not affect opioid dose |
| | ns | CB<WL+POTS | CB does not affect PEG score but decreases opioid dose |
| CB is harmful | CB+POTS > WL+POTS | CB+POTS > WL+POTS | CB increases PEG score and increases opioid dose |
| | CB+POTS > WL+POTS | ns | CB increases PEG score and does not affect opioid dose |
| | ns | CB+POTS > WL+POTS | CB does not affect PEG score and increases opioid dose |
| Individual costs/benefits should be evaluated | ns | ns | CB does not affect PEG score or opioid dose |
| | CB+POTS < WL+POTS | CB+POTS > WL+POTS | CB decreases PEG score but increases opioid dose |
| | CB+POTS > WL+POTS | CB+POTS < WL+POTS | CB increases PEG score but decreases opioid dose |

CB, cannabis; ns, not significant; PEG, Pain, Enjoyment and General Acitivity; POTS, Prescription Opioid Taper Support; WL, waitlist.

For 125 subjects per group, we would have 80% power to detect a minimum percent reduction of 13% in opioid dose for the CB+POTS group above and beyond that for the WL+POTS group. Even with only 100 subjects per group, we would have 80% power to detect a minimum percent reduction of 20% in opioid dose for the CB+POTS group above and beyond that for the WL+POTS group.

For our secondary outcome variables, which seek to address other behavioural measures such as OUD symptoms, pain interference, PEG score self-efficacy, pain-related function and psychological functioning (quality of life, depression, anxiety and sleep) in the active group compared with the WL+POTS group, we determined that with 100 participants in each group and 30% attrition (final n=70), we have 89% power to detect a difference in the slopes between baseline and the 6-month visit, at two-tailed p=0.05 level if the true difference in slopes is a 10% improvement on any of these measures in the CB group, and 0%–5% increase in the WL+POTS group.

More information is available in the trial statistical analysis plan (online supplemental file 3).

## Adverse events

Research coordinators will ask subjects to report adverse events (AEs) possibly related to cannabis, opioid use and the study intervention at all study visits and at the 12-month follow-up call. AEs will also be reviewed by the Data Safety Monitoring Board (DSMB) every 3 months. The DSMB will consist of one psychiatrist, one statistician and one addiction neuroscientist. Each member of the DSMB will not otherwise be associated with the trial. The DSMB charter is available as supplementary information (online supplemental file 4). Reporting and handling of AEs will be in concordance with IRB regulations and good clinical practice guidelines.

## Unblinding

We anticipate the need for assessor unblinding to be unlikely. Study physicians will be unblinded to manage cannabis-related AEs.

## Early termination of the trial

The DSMB will conduct a blind analysis of efficacy and safety data when half of the sample is enrolled. If there is a need to terminate this trial early, this decision will be made by the DSMB and submitted to the NIDA Project Officer.

## Patient and public involvement

Patients and the public were not involved in the development of the research question, the design, recruitment or conduct of the study, and the burden of the intervention was not assessed by the patients or the public.

## Ethics and Dissemination

This study has ethical approval by the Massachusetts General Brigham (MGB) Institutional Review Board (Protocol Number 2021P000871). Informed consent will be obtained from all participants by a trained member of study staff. Important protocol modifications will be submitted to the Institutional Review Board for approval and will be communicated with all participants. Results will be disseminated to participants by email and shared with the public through publication in peer-reviewed

journals and presentations at national conferences. Data will be deidentified in all cases.

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**Contributors** JG and AEE developed and designed the trial and obtained funding for the trial. JJ wrote the first draft of this manuscript. JG, AEE, CC, EG, AQ and JJ assisted with the study design. DAS and KP designed the statistical aspects of this protocol. All were involved in the revision of the manuscript. All authors approved the final version to be submitted.

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**Competing interests** AEE reported receiving grants from Charles River Analytics and non-financial support from Pfizer as well as serving as the chair of the data monitoring board of Karuna Pharmaceuticals outside the submitted work.

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**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.
**Version Date**: April 19, 2022

## 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.

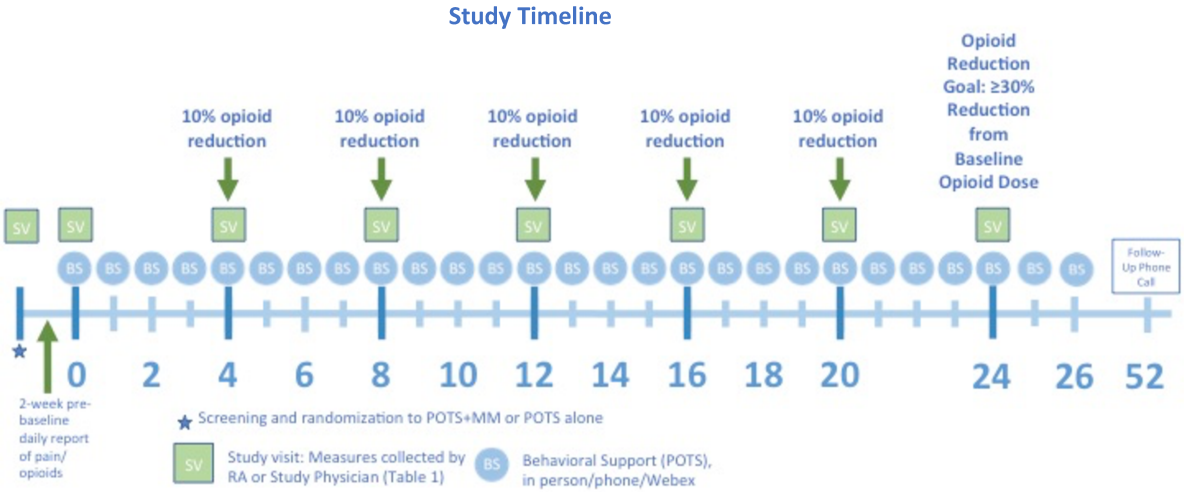
POTS sessions will be focused on individualized problem solving for behavioral self-management of pain and pros and cons of COT dose taper. During the 5 POTS sessions in study weeks 4-20 that coincide with the monthly study visits, study clinicians will work with participants to reduce opioid dose in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

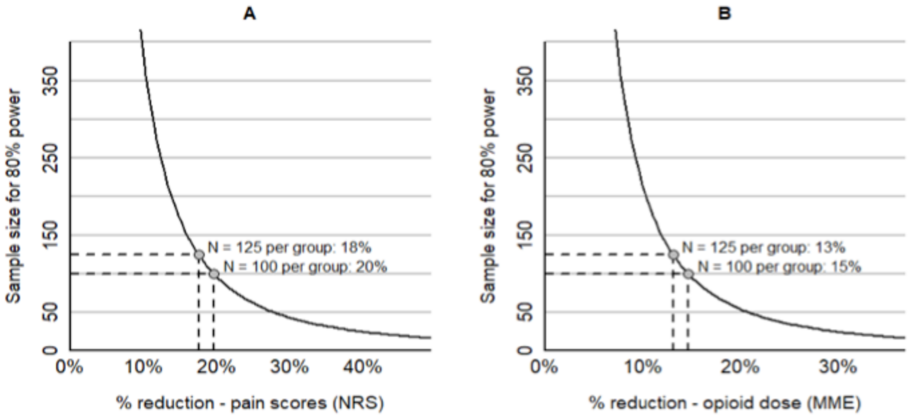
To assess cognitive performance, models will be the same as described above, except that the dependent variable will be change in scores on the cognitive tests (CVLT-III, CPT-3, WAIS-IV). We will co-vary for effects described above, as well as individual differences in baseline cognitive scores, and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

**Research Consent Form**
**General Consent Form Template**
**Version Date: February 2021**

Subject Identification

Protocol Title: 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, PhD, A. Eden Evins, MD

Site Principal Investigator:

Description of Subject Population: Adults with Chronic Non-Cancer Pain on Chronic Opioid Therapy (COT) ages 18-75

## About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

# Key Information

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. Your decision won't change the medical care you get within Partners now or in the future.

The following key information is to help you decide whether or not to take part in this research study. We have included more details about the research in the Detailed Information section that follows the key information.

## Why is this research study being done?

In this research study we want to learn more about how medical cannabis may affect opioid use and pain. The goal of this study is for all participants to taper their dose of opioid medications, while managing pain, and receive support from clinicians while doing this through the study



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|---|---|---|
| **Consent Form Title: Opioid Consent Form 2.2.22_CLEAN** | | |
| **IRB Protocol No: 2021P000871** | **Sponsor Protocol No: Opioid Protocol 2/2/22** | |
| **Consent Form Valid Date: 3/7/2022** | **IRB Amendment No: AME18** | **Sponsor Amendment No: N/A** |
| **Consent Form Expiration Date: 6/25/2022** | **IRB Amendment Approval Date: 3/7/2022** | |

program. Tapering from a medication means gradually reducing your dose. Research has shown that tapering to a reduced dose of opioids may have significant health benefits.

The program is called Prescription Opioid Tapering Support (POTS), which is a behavioral support program aimed at helping you reduce your daily dose of opioid medication.

Everyone in this study will participate in the POTS program, and some people may be able to start using Medical Cannabis (MM) in addition.

## Who will take part in this research?

We are asking you to take part in this study because you are an adult who uses opioid medication to treat your chronic pain.

About 250 people will take part in this study. We plan to enroll participants at Massachusetts General Hospital, Cambridge Health Alliance, and Maine Medical Center.

The National Institute on Drug Abuse is paying for this study to be done.

## How long will you take part in this research study?

If you decide to join this research study, it will take you about 6 months to complete the study. During this time, we will ask you to make 8 study visits to MGH. After the screening visit, we will have you come in for a baseline study visit. You will then come in for visits at 4, 8, 12, 16, 20, and 24 weeks after the baseline visit. The POTS program will take place weekly throughout the study (over 26 weeks).

We will also schedule a call with you one year after your baseline visit to check in on your overall health, medications, and pain levels.

# Detailed Information

## What will happen if you take part in this research study?

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures.

If you decide to join this research study, we will ask that you:

- Participate in the Prescription Opioid Tapering Support (POTS) program (over 26 weeks)
- Complete questionnaires and participate in interviews asking you about your physical health, mental health, medications, substance use, and overall functioning
- Complete cognitive testing via games on a tablet
- Provide urine samples to be tested for drugs and pregnancy (pregnant women are not allowed to participate)
- Complete a daily survey about your pain and medications (every day for 28 weeks)
- Confirm scheduled appointments through text message reminders

If you are eligible for this study, you will be randomly assigned to either the active study group (MM+POTS) or a waitlist control group (POTS alone). If you are in the active study group, you will be able to start using medical cannabis right away. If you are in the waitlist control group, you will be asked to abstain from using cannabis, and you will have the option to start using medical cannabis after the first 6 months of the study. Medical marijuana and medical marijuana certificates will not be provided as part of the study.

The POTS program is designed to provide opioid taper support and will be offered weekly to all participants. Sessions will be conducted over videoconference with a trained clinician and other participants. POTS sessions will be focused on individualized problem solving for behavioral self-management of pain and pros and cons of opioid dose taper. POTS sessions will be video recorded. During the 5 regular clinic visits 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. Any opioid dose decrease is optional. Opioid doses will not be increased during the study.

Screening Visit:
The purpose of the screening visit is to determine if you are eligible for this study. During your screening visit, we will ask you to:

- Complete several questionnaires
- Participate in interviews asking about physical health, mental health, and substance use
- Provide a urine sample (which will be tested for drugs and pregnancy)
- Demonstrate how to complete daily surveys on your phone to record your opioid medications and pain levels

**Assignment to Study Group**
If after the screening visit, you qualify to take part in this study, we will assign you by chance to the MM group or the control group. You and the study doctor cannot choose your study group.

We use control groups in research studies to learn if the effects seen in research subjects are truly from a particular treatment.

If you are assigned to the Active Group, you will be able to start using medical cannabis to see if it helps treat your pain or not.

If you are assigned to the Waitlist Group, you will be asked to abstain from cannabis for the first 6 months of the study. If you choose to, you may use cannabis after the 6-month waiting period.

**Daily Surveys**

During this study, you will be asked to complete daily surveys to keep track of your marijuana use, opioid use, pain, and health using REDCap, a secure web-based application designed for data collection for research studies.

Study staff will provide instructions for how to access and complete the daily surveys at your screening visit.

You will receive text message reminders containing the survey link when it is time to complete the daily survey. You will be asked to input a four-digit code before completing the survey for your privacy.

This application will NOT be used to collect and report any emergencies, side effects, or adverse events you may experience during the study. If there is something you need to discuss with the site, you should contact study staff directly.

**Text Message Reminders**

Text messages by mobile/cell phones are a common form of communication. This research study involves sending you text messages that are relevant to the research study. Texting over mobile/cell phones carries security risks because text messages to mobile/cell phones are not encrypted. This means that information you send or receive by text message could be intercepted or viewed by an unintended recipient, or by your mobile/cell phone provider or carrier.

Below are some important points about texting in this research study.

- Text messages are not encrypted, and therefore carry security risks. This research study and Mass General Brigham Healthcare are not responsible for any interception of messages sent through unencrypted text message communications.

- You will be responsible for all fees charged by your carrier's service plan for text messaging. This research study and Mass General Brigham Healthcare are not responsible for any increased charges, data usage against plan limits or changes to data fees from the research texts
- Text messaging should not be used in case of an emergency. If you experience a medical emergency, call 911 or go to the nearest hospital emergency department.
- You may decide to not send or receive text messages with staff associated with this research study at any time. You can do this in person or by sending the research number a text message that says, "Stop Research Text."
- Your agreement applies to this research study only. Agreeing to other texts from Mass General Brigham Healthcare, for example appointment reminders, is a separate process. Opting out of other texts from Mass General Brigham Healthcare is a separate process as well.
- It is your responsibility to update your mobile/cell phone number with this research study in the event of a change.

I have had the chance to ask questions about texting with staff associated with this research study. I have been informed of the risks and other information covered above and consent to the use of unencrypted text communications associated with this research study.

| **Subject** | **Date** | **Time (optional)** |
|---|---|---|

Baseline Visit:
Approximately, two weeks after your screening visit or once you receive your medical cannabis card if you are in the active group, you will come in for a baseline assessment. During this visit, you will:

- Complete several questionnaires
- Participate in interviews asking about physical health, mental health, and substance use
- Provide a urine sample (which will be tested for drugs and pregnancy)
- Complete cognitive testing via games on a tablet
- Begin the Prescription Opioid Tapering Support (POTS) groups

Visits at (approximately) Weeks 4, 8, 12, 16, 20, and 24:
Approximately, every 4 weeks after the Baseline visit, you will:

- Possibly reduce your opioid dose by approximately 10% with consultation with study clinicians
- Complete questionnaires

- Participate in interviews asking about physical health, mental health, and substance use
- Complete cognitive testing via games on a tablet
- Provide a urine sample (which will be tested for drugs and pregnancy)

12 Month Follow Up Call:
Approximately 12 months after completing your baseline visit, you will complete a follow up call. We will ask you about:

- Your overall health, including physical and mental health
- Your current medications
- Your current substance use

Throughout the Study:
Every day of the study (for 28 weeks), you will be asked to complete a short survey on your smartphone/computer asking you about your opioid medication dose and your pain levels.

Every 4 weeks of the study (for weeks 4-24), you will have a study visit (either in person or via zoom), in which you will discuss the possibility of reducing your opioid dose by 10%. You can pause your opioid dose taper at any point. However, you will not be allowed to increase your opioid dose during this study.

We will ask that you tell us about any important changes in your health, even if they do not seem relevant to the research. Partners has an electronic system that lets your study doctors know if you are admitted to a Partners Hospital, or if you visit a Partners Hospital Emergency Department. We want to make sure the study doctors know about any possible problems or side effects you experience while you are taking part in the study.

After You Complete the Study:
Study staff will coordinate return to your primary care physician and consult on additional therapy that may help you control your pain and maintain your reduced opioid dose.

**Urine Shipments**
We will collect urine samples at every study visit, which will be tested for drugs and pregnancy (in females). With your permission, a small quantity (2 teaspoons) of the urine sample will be shipped to collaborators at a lab who can quantify cannabinoids in the urine. We will only ship your sample if a) you agree to having your samples shipped AND b) you report using marijuana products since your last study visit, and/or c) your qualitative urine drug test is positive for THC.

**Do we have your permission to ship urine samples for quantitative analysis?**

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**General Consent Form Template**
**Version Date: February 2021**

Subject Identification

☐ **YES** ☐ **NO** **Initials**_____

**Medical Records and Prescription Monitoring Program (PMP)**

This study will require that we access your record through the Prescription Monitoring Program to verify opioid medications and other medications monitored by the PMP.

This study will require that we access your electronic medical record to verify concomitant medications and doses prescribed by caregivers in the MGB, CHA, and MMC systems of care. As part of study procedures, you will provide contact information for your prescribing physician to the study team. The study team will contact the provider(s) primarily responsible for your opioid prescribing at the time of enrollment to inform them of your participation in the study, and again each time you agree to a new opioid dose. Decisions regarding opioid dose adjustment are subject to approval by the prescribing physician.

**Information Storage**
Study information collected from you will be stored in a database on a password-protected computer. This information will not become part of your medical record.

We will assign all information a unique code. The key to the code will be kept on encrypted computer. Only the researchers from our research study will be able to use the computer. The code linking test results to subject identity will only be accessible to study staff. If you decide to drop out of this research study at a later time, please contact one of the research coordinators for this study:

Julia Jashinski: 617-643-1984; jjashinski@mgh.harvard.edu

## What are the risks and possible discomforts from being in this research study?

Taking part in this research study has some risks that you should consider carefully. Important risks and possible discomforts to know about include:

Reducing opioid dose:
Most people don't get very physically uncomfortable with withdrawal while tapering gradually. It is possible you may experience increased pain, restlessness, sweating, body aches, irritability, diarrhea, stomach upset, and sometimes sleep problems.

Medical Cannabis:



| | | |
|---|---|---|
| **Consent Form Title: Opioid Consent Form 2.2.22_CLEAN** | | |
| **IRB Protocol No: 2021P000871** | **Sponsor Protocol No: Opioid Protocol 2/2/22** | |
| **Consent Form Valid Date: 3/7/2022** | **IRB Amendment No: AME18** | **Sponsor Amendment No: N/A** |
| **Consent Form Expiration Date: 6/25/2022** | **IRB Amendment Approval Date: 3/7/2022** | |

Cardiovascular effects of cannabis largely depend on several factors, including dose, frequency, route of administration, and duration of use. THC can have diverse effects on heart rate and blood pressure, and although present knowledge about the relationship between cannabis or medical cannabis use and cardiovascular disease outcomes is still limited

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). Some participants may experience adverse events including increased anxiety, paranoia, sleeping difficulties, increases in suicidal thoughts, or temporary psychosis. Some people may develop symptoms of cannabis use disorder.

Other risks of medical cannabis may exist that are not known yet. We will inform you of any risks that we learn about as a part of doing this study

Loss of confidentiality:
We will not share your identity with anyone outside the Partners/Mass General Brigham institutions. However, we cannot guarantee your total confidentiality.

We will numerically code all data and remove all personal identifiers from the data. We will store all data in password protected databases. Subject information will be accessible only to research staff. Information about study participants will not leave our institution in any form that would identify individual subjects.

## What are possible benefits from being in this research study?

We cannot promise any benefits to you from taking part in this research study. Possible benefits may include reduced opioid dose and better pain management. Others who take opioids for chronic pain may benefit in the future from what we learn in this study.

## What other treatments or procedures are available for your condition?

Other treatments or procedures that are available to treat chronic pain include:

- Medications:
  - Over-the-counter medications (acetaminophen, aspirin, ibuprofen, naproxen)
  - Muscle relaxants (cyclobenzaprine, tizanidine, baclofen)
  - Anti-anxiety drugs (lorazepam, diazepam)
  - Antidepressants (amitriptyline, doxepin, imipramine, venlafaxine, duloxetine)

- Prescription anti-inflammatory drugs (celecoxib, piroxicam, indomethacin, meloxicam)

- Other treatments:
  - Steroid injections at the site of pain
  - Surgery
  - Physical and occupational therapy
  - Acupuncture
  - Massage
  - Hot/cold therapy
  - Exercise

## If you have questions or concerns about this research study, whom can you call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Jodi Gilman, Ph.D. is the person in charge of this research study. You can call her at 617-643-7293 Monday through Friday 9AM to 5PM. If necessary, you can reach her after hours at jgilman1@mgh.harvard.edu.

If you have questions about the scheduling of appointments or study visits, please contact one of the research coordinators for this study:

Julia Jashinski: 617-643-1984; jjashinski@mgh.harvard.edu

If you want to speak with someone **not** directly involved in this research study, please contact the Mass General Brigham IRB office. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research
- Any pressure to take part in, or to continue in the research study

## How may we use and share your samples and health information for other research?

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**General Consent Form Template**
**Version Date: February 2021**

Subject Identification

The information we collect in this study may help advance other research. If you join this study, we remove all information that identifies you (for example, your name, medical record number, and date of birth) and use these de-identified samples and data in other research. It won't be possible to link the information or samples back to you.

## Can you still get medical care within Mass General Brigham if you don't take part in this research study, or if you stop taking part?

Yes. Your decision won't change the medical care you get within Mass General Brigham now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

## What should you do if you want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

## Will you be paid to take part in this research study?

You will be paid following each study visit by check that will be mailed to you. You will earn $20 for the screening visit, and $40 for each study visit afterwards (7 study visits). You will receive $30 for completing the 1-Year Phone Call. You will also earn $20 for each POTS session (26 in total). You will be paid $1 per day for completing the daily diary and can earn $10 for full weeks of consecutive entries (up to $280). You will also be paid up to $5 per study visit for travel costs. In total, you can earn up to $1,130 by participating in this study. Regardless of which group you are in (POTS+MM or POTS alone), you can earn the same amount of money. Please see the detailed table here. In accordance with Partners Policy, to receive payment each participant is asked to provide us their Social Security Number or Tax ID number. All payments will be made via check following each study visit. Receiving compensation from participating in this study may impact your tax liability and/or eligibility for federal or state benefits (i.e., SSDI, SNAP).

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Subject Identification

| Week | Visit | | |
|---|---|---|---|
| -2 | Screening | V0 | $20 |
| 0 | Baseline | V1 | $40 |
| 4 | In person | V2 | $40 |
| 8 | In person | V3 | $40 |
| 12 | In person | V4 | $40 |
| 16 | In person | V5 | $40 |
| 20 | In person | V6 | $40 |
| 24 | In person | V7 | $40 |
| 52 | Phone call | | $30 |
| | Dosing Diaries (28 weeks x $10/week) | | $280 |
| | POTS sessions (26 sessions x $20/session | | $520 |
| Total | | | $1130 |

## Will I have to pay if I take part in this research study?

There is no cost to you for taking part in this study. The cost of all of the tests and procedures done for research will be paid for by study funds.

You/your health insurer will be responsible for the cost of the MM because this would be needed for your care even if you are not in the study.

Charges for any ongoing or routine medical care you receive outside this study will be billed to you or to your insurance company in the usual way. You will be responsible for any deductibles or co-payments required by your insurer for your routine medical care.

## What happens if you are injured as a result of taking part in this research study?

**Partners HealthCare System**
**Research Consent Form**

Subject Identification

**General Template**
**Version Date: December 2008**

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the beginning of this consent form.

## If you take part in this research study, how will we protect your privacy?

Federal law requires Mass General Brigham to protect the privacy of health information and related information that identifies you. We refer to this information as "identifiable information."

### In this study, we may collect identifiable information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

### Who may see, use, and share your identifiable information and why they may need to do so:

- Mass General Brigham researchers and staff involved in this study
- The sponsor(s) of the study, and people or groups it hires to help perform this research or to audit the research
- Other researchers and medical centers that are part of this study
- The Mass General Brigham ethics board or an ethics board outside Mass General Brigham that oversees the research
- A group that oversees the data (study information) and safety of this study
- Non-research staff within Mass General Brigham who need identifiable information to do their jobs, such as for treatment, payment (billing), or hospital operations (such as assessing the quality of care or research)
- People or groups that we hire to do certain work for us, such as data storage companies, accreditors, insurers, and lawyers
- Federal agencies (such as the U.S. Department of Health and Human Services (DHHS) and agencies within DHHS like the Food and Drug Administration, the National

Institutes of Health, and the Office for Human Research Protections), state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records

- Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
- Other:

Some people or groups who get your identifiable information might not have to follow the same privacy rules that we follow and might use or share your identifiable information without your permission in ways that are not described in this form. For example, we understand that the sponsor of this study may use your identifiable information to perform additional research on various products or conditions, to obtain regulatory approval of its products, to propose new products, and to oversee and improve its products' performance. We share your identifiable information only when we must, and we ask anyone who receives it from us to take measures to protect your privacy. The sponsor has agreed that it will not contact you without your permission and will not use or share your identifiable information for any mailing or marketing list. However, once your identifiable information is shared outside Mass General Brigham, we cannot control all the ways that others use or share it and cannot promise that it will remain private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your identifiable information. Your permission to use and share your identifiable information does not expire.

The results of this research study may be published in a medical book or journal, or used to teach others. However, your name or other identifiable information **will not** be used for these purposes without your specific permission.

## Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your identifiable information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your identifiable information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

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If you withdraw your permission, we will not be able to take back information that has already been used or shared with others, and such information may continue to be used for certain purposes, such as to comply with the law or maintain the reliability of the study.

You have the right to see and get a copy of your identifiable information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

## Informed Consent and Authorization

**Statement of Person Giving Informed Consent and Authorization**

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

### Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

| _____ | _____ | _____ |
|---|---|---|
| Subject | Date | Time (optional) |

### Signature of Study Doctor or Person Obtaining Consent:

**Statement of Study Doctor or Person Obtaining Consent**

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

| _____ | _____ | _____ |
|---|---|---|
| Study Doctor or Person Obtaining Consent | Date | Time (optional) |



| | | |
|---|---|---|
| **Consent Form Title: Opioid Consent Form 2.2.22_CLEAN** | | |
| **IRB Protocol No: 2021P000871** | **Sponsor Protocol No: Opioid Protocol 2/2/22** | |
| **Consent Form Valid Date: 3/7/2022** | **IRB Amendment No: AME18** | **Sponsor Amendment No: N/A** |
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**Research Consent Form**
**General Consent Form Template**
**Version Date: February 2021**

Subject Identification

Consent Form Version: 02.2.22



| | | |
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# Evaluation of Medical Cannabis and Prescription Opioid Taper Support for Reduction of Pain and Opioid Dose in Patients with Chronic, Non-Cancer Pain

**NCT04827992**

**Version 3**
**First version: 12/20/2021**
**Latest version: 5/02/2022**



Jashinski J, *et al. BMJ Open* 2022; 12:e064457. doi: 10.1136/bmjopen-2022-064457

## Table of contents

## Glossary

| Abbreviation | Term |
|---|---|
| APA | American Psychological Association |
| CNCP | Chronic non-cancer pain |
| CUD | Cannabis use disorder |
| GEE | Generalized estimating equations |
| CB | Cannabis |
| MME | Morphine milligram equivalents |
| OUD | Opioid use disorder |
| PMP | Prescription monitoring program |
| POTS | Prescription opioid tapering support |
| WL | Waitlist |

## Design

The study will examine the efficacy of the addition of cannabis (CB) to prescription opioid tapering support (POTS) to help reduce pain and opioid use for patients with chronic non-cancer pain (CNCP). The study will contrast participants randomized to a 24-week period of either (1) receiving both POTS and CB post-baseline (**CB+POTS)** versus (2) receiving POTS post-baseline while wait-listed for receiving CB (**WL+POTS**).

The study aims to enroll up to 250 participants, adults aged 18 to 75 with CNCP endorsing >6 months of pain (neuropathic, nociceptive, or centralized pain) on stable prescription opioid doses of $\geq$ 25 MME/day for >90 days. Participants will be randomized in a 1:1 ratio at the therapy-group level (Therapy groups will consist of up to 6 participants, and all participants in a group will be randomized to the same condition to avoid cross-contamination). Therefore, it is expected that the CB+POTS and WL+POTS groups will each have up to 125 participants.

## Analytic approach

### Primary outcomes

Our co-primary outcomes will be…

1. The summed score (ranging from 0 to 30) of the 3-item Pain Enjoyment General Activity (PEG) scale (Krebs et al., 2009), where higher scores indicate greater pain severity and/or interference.
    - The PEG scores will be collected daily via self-report through a smartphone app from the baseline assessment to the end of the 24-week period (i.e., up to 168 observations per participant). All post-baseline daily observations for PEG scores will be analyzed.
2. Prescription monitoring program (PMP) verified opioid dose, in mean daily morphine milligram equivalents (MME).
    - We expect little variation in opioid dose until the conclusion of the treatment regime. Therefore, we will only analyze opioid doses reported during baseline and at week 24 of the study.
    - Note that if participants and their doctors decide to reduce dose at week 24, we will use the reduced dose even if the new dose cannot immediately be implemented (e.g., due to delays in scheduling and refilling prescriptions) to ensure accurate representation of change.

*Statistical model*

We will analyze both outcomes using a linear regression model. Coefficients and standard errors for the linear model will be obtained using generalized estimating equations (GEE; Liang & Zeger, 1986). Note the GEE approach provides robust standard errors and well-calibrated p-values (i.e., a family-wise error rate of 0.05) even when distributional assumptions are violated and when heteroscedasticity is present. We will assume data are clustered over participants, and that the observations for a participant (pooled over each month in the case of daily PEG scores), are uncorrelated (The GEE method is also robust to misspecification of the correlation structure for a participant's observations). The p-value for the primary contrast will be computed via a z-test using the mean estimate and a robust standard error computed via the sandwich estimator. The primary contrast testing for a constant effect of CB above and beyond POTS will be deemed statistically significant for $p < 0.025$, thereby ensuring an overall family-wise error rate of 5% despite two primary outcomes.

For each outcome, the key confirmatory effect of interest will be…

PEG scores: A dummy-coded contrast between WL+POTS (the referent, coded as 0) and CB+POTS (coded as 1), testing whether a constant effect of CB exists, averaged over all time points. Additionally, we will include the following covariates: (a) A quadratic trend for change over days, consisting of a z-score for days since baseline (the linear component) along with the same z-score raised to the power of two (the quadratic component); (b) A participant's PEG score at the baseline

visit (converted to a z-score); (c) A participant's prescription opioid dose (MME) at the baseline visit (converted to a z-score). In other words, we assume a conservative additive model, adjusting for baseline levels and with main effects for a) the impact of CB and b) change over time, but no treatment by time interaction.

Opioid dose: The treatment (WL+POTS versus CB+POTS) by time (baseline versus week 24) interaction, testing whether there is a significant reduction in opioid dose at week 24 for CB+POTS above and beyond any reduction for WL+POTS. Main effects will be dummy-coded (WL+POTS coded as 0, CB+POTS coded as 1; baseline coded as 0, week 24 coded as 1), and the interaction will be defined as the product of the two. Additionally, we will include as a covariate a participant's PEG score at the baseline visit (converted to a z-score).

*Missing data*

The GEE method is robust to data missing completely at random (MCAR), but it is more likely that data will be missing at random (MAR). Therefore, we will address missingness using multiple imputation via chained equations (MICE). However, participants who have fewer than 14 days (two weeks) of non-missing data will be excluded from the analysis (i.e., participants with less than 8.3% of the total number of possible observations will be excluded). All missing post-baseline outcome values will be imputed for opioid dose. However, for daily PEG scores, when outcome data is missing over multiple days in a row, the first and final day in the run will be imputed, with the remainder excluded (to reduce computational burden and ensure imputed values do not have excessive influence on analyses). Missing outcome data will be imputed 40 times, using, at a minimum, the following predictors:

- A participant's age in years;
- A participant's biological sex (male versus female);
- A participant's prescribed opioid dose (MME) at the baseline visit;
- Number of baseline opioid use disorder (OUD) symptoms;
- A participant's PEG score at the baseline visit;
- A participant's type of pain (neuropathic, nociceptive, or centralized pain);
- The outcome value on the previous entry (i.e., lag 1).

Continuous variables (except for the lag 1 term) will be converted to z-scores. Categorical variables will be first effects coded and then converted to z-scores. If additional variables are determined prior to data analysis to be predictive of missingness, they will also be included. Analyses will be run using complete and imputed data for each imputation iteration, and results will be pooled according to Rubin's rule.

*Intent-to-treat analysis*

We understand that there may be some contamination between groups (e.g., some patients in the WL+POTS group may use CB, and some patients in the CB+POTS group may decide not to use CB). As this is a pragmatic trial, our primary analysis will be an intent-to-treat analysis, in which all participants will be analyzed by group (CB vs WL+POTS). This intent-to-treat analysis will *be representative of real-world, ecologically valid outcomes*, in which a clinician would recommend CB to a patient, and then the patient would come to a decision about whether CB was helpful, 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 CB has a biological effect on pain and/or opioid use.

*Sensitivity analyses*

We will conduct a minimum of 4 sensitivity analyses.

1. We will examine if the direction and significance of the primary contrast between CB+POTS and WL+POTS is robust to the inclusion of additional covariates, specifically age (in years), biological sex (male versus female), number of baseline OUD symptoms, and pain type (neuropathic, nociceptive, or centralized pain). Categorical effects will first be effect-coded (-1 for the referent level, 1 for the specified level, and 0 otherwise) and then all covariates will be converted to z-scores.
2. We will test our assumption of an additive model for PEG scores by fitting a model that includes a treatment by time interaction (i.e., the product of the contrast between CB+POTS and WL+POTS and the two covariates for the quadratic time trend). We will conduct an analysis of variance comparing the simpler additive model to the more complex interaction model – if the associated Wald test is significant at $p < 0.05$ following a correction using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995), this will indicate the presence of a treatment by time interaction.
3. We will examine if the direction and significance the primary contrast between CB+POTS and WL+POTS is robust to our treatment of missing data by fitting the statistical model to the observed data only.
4. We will conduct an as-treated analysis to address the risk of bias by indication (e.g., patients in the WL+POTS group who are suffering worse pain may be more likely to use CB). We will examine CB without regard to treatment group assignment, instead examining those who used CB regularly (weekly or more) vs those who did not use (verified by negative urine screens and no self-reported use). We will correct for “confounding by indication” by weighting data by the inverse probability of being in the CB or non-user group.

Note it may be necessary to include additional sensitivity analyses to address unanticipated developments during the course of the study.

*Clinical significance*

Examination of PEG scores and opioid does means that a combination of clinical outcomes is possible (see Table 1), which will indicate whether *CB is helpful* (e.g. decreases opioid doses and/or PEG scores), *CB is harmful* (e.g. increases opioid dose and/or PEG scores), or that *CB has no clear effect on opioid dose/PEG scores (no notable changes, or increases one outcome and decreases another)*. In the third condition, an exploratory analysis will evaluate costs/benefits of CB to the individual patient, measured via the proposed secondary outcomes.

Table 1: Decision table for each possible outcome

| Decision | PEG scores at 6 months compared to Baseline | Opioid dose at 6 months compared to Baseline | Meaning |
|---|---|---|---|
| **CB is beneficial** | CB+POTS < WL+POTS | CB+POTS < WL+POTS | CB reduces PEG score AND decreases opioid dose |
| | CB+POTS < WL+POTS | ns | CB reduces PEG score and does not affect opioid dose |
| | ns | CB < WL+POTS | CB does not affect PEG score but decreases opioid dose |
| **CB is harmful** | CB+POTS > WL+POTS | CB+POTS > WL+POTS | CB increases PEG score and increases opioid dose |
| | CB+POTS > WL+POTS | ns | CB increases PEG score and does not affect opioid dose |
| | ns | CB+POTS > WL+POTS | CB does not affect PEG score and increases opioid dose |
| **Individual costs/benefits should be evaluated** | ns | ns | CB does not affect PEG score or opioid dose |
| | CB+POTS < WL+POTS | CB+POTS > WL+POTS | CB decreases PEG score but increases opioid dose |
| | CB+POTS > WL+POTS | CB+POTS < WL+POTS | CB increases PEG score but decreases opioid dose |

**Secondary Outcomes**

Our secondary outcomes will be…

1. The summed score (ranging from 14 to 70) of the 14-item Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF; Schechter, Endicott, & Nee, 2007), where lower scores indicate greater dissatisfaction with life.
2. The T-score (mean of 50 and SD of 10) of the 8-item Depression subscale of the PROMIS-29 (Cella et al., 2010), where higher scores indicate a greater degree of depression.
3. The T-score (mean of 50 and SD of 10) of the 7-item Anxiety subscale of the PROMIS-29 (Cella et al., 2010), where higher scores indicate a greater degree of anxiety.
4. The number of symptoms (ranging from 0 to 11) for Opioid Use Disorder (OUD), based on the DSM-5 Opioid Use Disorder Checklist (American Psychiatric Association [APA], 2013).
5. The number of symptoms (ranging from 0 to 11) for Cannabis Use Disorder (CUD), based on the DSM-5 Cannabis Use Disorder Checklist (APA, 2013).
6. Self-reported opioid dose in MME units collected daily via self-report through a smartphone app and then averaged over each month (opioid dose is not expected to vary substantially day to day).

The secondary outcomes will be collected monthly during in-person study visits over the 24-week period (i.e., up to 7 observations per participant).

*Statistical model*

We will use the same linear regression model, design matrix, and GEE method as proposed for our primary outcomes. Specifically, we will use the same statistical model used with the PEG scores (note by necessity the linear and quadratic time trends will be defined over monthly visits). The primary contrast testing for a constant effect of CB above and beyond POTS will be deemed statistically significant for $p < 0.05$ following an adjustment across all secondary outcomes using the Benjamini-Hochberg method, thereby ensuring a false-discovery rate of 5% despite multiple comparisons over nine secondary outcomes.

*Missing data*

We will use the same approach (multiple imputation via chained equations) as specified for the primary outcomes (specifically, the approach used with PEG scores).

*Sensitivity analyses*

At a minimum, the 4 sensitivity analyses proposed for the primary outcomes will also be run for each secondary outcome. Again, note it may be necessary to include additional sensitivity analyses to address unanticipated developments during the course of the study.

**Power**

While final analyses will rely linear regressions robust to clustering and heteroscedasticity, because the key contrast of interest is the mean difference between CB+POTS and WL+POTS, power can be approximated via standard methods for independent samples t-tests. The target sample size was 125 participants per group, or 100 participants under a worse-case scenario of 20% attrition. A power curve for each outcome was computed, plotting the required sample size for 80% power against the associated minimum detectable percent reduction in the outcome measure.

- *PEG scores*: Power curve estimates were based on preliminary data, 3205 daily pain scores (a component of PEG scores) reported by 46 participants in the previous CB study over a period of 84 days (roughly 3 months). The mean (6.3) and standard deviation (3.1) for pain scores in the first two weeks was used to compute percent reduction. For 125 participants per group, we would have 80% power to detect a minimum percent reduction of 18% in PEG scores for the CB+POTS group above and beyond that for the WL+POTS group. Even with only 100 participants per group, we would have 80% power to detect a minimum percent reduction of 20% in PEG scores for the CB+POTS group above and beyond that for the WL+POTS group.
- *Opioid dose*: Power curve estimates were based on opioid dose data for the 145 PEG score patients extracted from Massachusetts General Hospital's 2017 records. We used the mean (88) and standard deviation (32) in morphine milligram equivalents (MME) for compute percent reduction. For 125 participants per group, we would have 80% power to detect a minimum percent reduction of 13% in opioid dose for the CB+POTS group above and beyond that for the WL+POTS group. Even with only 100 participants per group, we would have 80% power to detect a minimum percent reduction of 20% in opioid dose for the CB+POTS group above and beyond that for the WL+POTS group.

## Software

All analyses will be done using the statistical software R (version 4.1.1; R Core Team, 2021) and integrated development environment RStudio (version 2020.9.0.351; RStudio Team, 2021). Data will be prepared using the R packages 'dplyr' (version 1.0.7; Wickham, François, Henry, & Müller, 2021) and 'tidyr' (version 1.1.4; Wickham, 2021). Models will be fit using the R package 'geepack' (version 1.3-2; Højsgaard, Halekoh, & Yan, 2006). Missing data will be imputed using the R package 'mice' (version 3.13.0; Van Buuren & Groothuis-Oudshoorn, 2011). Reproducible code and de-identified data will be organized using the R package 'targets' (version 0.8.1; Landau, 2021) and Gitlab (version 14.6.7; Gitlab Team, 2022).



Jashinski J, *et al. BMJ Open* 2022; 12:e064457. doi: 10.1136/bmjopen-2022-064457

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**DSMB Charter**

Evaluation of Medical Cannabis and Prescription Opioid Taper Support for Reduction of Pain and Opioid Dose in Patients with Chronic Non-Cancer Pain

2021P000871

MPIs: Jodi Gilman, PhD, A. Eden Evins, MD

NIDA R01 DA051540-01A1

## A. Safety monitoring

An independent Data and Safety Monitoring Board (DSMB) will be appointed for this study, to assess the safety of the study by determining whether there is an unacceptable level of risk due to study procedures and whether an increased number of adverse events occur.
The DSMB will be established to analyze interim results to assess the safety of the trial at regular intervals for the duration of the study by determining whether an increased number of adverse events occur among study participants receiving drug compared to participants
receiving placebo.

The board will include a statistician, an addiction expert, and a psychiatrist. Each member of the DSMB will not otherwise be associated with the trial. Safety data will be reviewed by the Data and Safety Monitoring Board Data every 6 months after the recruitment period begins. The DSMB will receive summary reports on recruitment, retention and description of all adverse events and review them at each biannual DSMB meeting. The DSMB will receive all communication with the IRB. Subject information provided to the board will be identified only with study IDs to protect the confidentiality of subjects. The DSMB will assess interim results to determine whether the active drug treatment is associated with substantial risk, including higher rate of adverse outcomes when compared with the placebo group.

## B. Outcomes monitoring

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

| **DSMB Role** | **Name and title** | **Affiliation / Institution** | **Contact details** | **Summary of expertise** |
|---|---|---|---|---|
| DSMB Chair and Medical Safety Officer | David Mischoulon, MD | MGH | dmischoulon@mgh.harvard.edu | depression, complementary and alternative medicine |
| DSMB Biostatistician | Susanne Hoeppner, PhD | Harvard Medical School | shoeppner@mgh.harvard.edu | biostatistician and epidemiologist |
| DSMB Addiction Expert | Amy Janes, PhD | Harvard Medical School | ajanes@mclean.harvard.edu | neuroimaging, brain function, drug use and relapse. |

Trial investigators will not be members of the DSMB.