Mass General Brigham

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

Subject Identification

Cannabidiol on Reward- and Stress-related Neurocognitive Processes in Individuals With Opioid Use Disorder

NCT04982029

Document Date: 4/14/22

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator: Joji Suzuki

Project Title: Cannabidiol on reward-and stress-related neurocognitive processes in individuals with opioid use disorder: A double-blind, placebo-controlled, cross-over trial

Version Date: 4/14/2022

For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

Opioid use disorder (OUD) remains a major public health crisis: Drug overdoses continue to contribute over 70,000 death annually, with opioids, in particular synthetic opioids, playing the largest role in this ongoing epidemic[1]. Individuals with opioid use disorder (OUD) therefore continue to die each year despite the availability of effective therapies.

Medication treatment for OUD (MOUD) reduces overdose mortality: MOUDs (i.e. buprenorphine and methadone) are gold-standard treatments for OUD because they will reduce overdose mortality by as much as 70%[2]. Unfortunately, close to 50% will relapse and discontinue treatment within 6 months[3].

Neurocognitive deficits play a critical role in relapse to illicit opioids: Individuals with OUD have a strong attentional bias towards drug-related cues over neutral cues. This process is automatic, fast, and operates largely outside of conscious awareness. With greater attention paid to these cues, subjective cravings then emerge[4]. The resulting cravings in turn enhances the attentional bias even further, creating a self-sustaining cycle that can lead to relapse. Furthermore, individuals with OUD demonstrate poor decision making, preferring smaller immediate rewards over larger delayed rewards[5]. Finally, individuals with OUD demonstrate heightened reactivity to stressors[6]. Together, these neurocognitive deficits contribute to the risk of relapse. A problematic feature of these deficits is their persistence long after abstinence is achieved, highlighting the difficulty in sustaining recovery in the long-term. As such, these deficits are important targets to improve treatment outcomes of individuals being treated with MOUD.

There are no evidence-based psychosocial or pharmacologic adjuncts to existing medications to improve outcomes: Psychosocial interventions such as cognitive-behavioral therapy and drug counseling teach individuals to manage cravings, and have robust empirical support with other substance use disorders. However, in numerous clinical trials, these psychosocial treatments have been largely ineffective for those

with OUD[8]. There currently are no evidence-based pharmacologic adjuncts to medication treatment to improve outcomes. As such, there is a critical need to identify novel adjunct interventions for individuals with OUD currently engaged in medication treatment.

CBD has emerged as a possible intervention: We will address this need by conducting a study of CBD which has promise as an adjunctive treatment to MOUD. In humans, CBD administration has been shown to reduce attentional bias for tobacco-related cues in individuals with tobacco use disorder, as well as for cannabis-related cues among individuals who are regular cannabis smokers. CBD also significantly reduced cue-induced cravings compared to placebo in those with OUD but not taking MOUD[9,10]. In both animal and human studies, CBD appears to target brain regions that mediate neural responses to drug-related cues, indicating the relevance of CBD in modulating the attentional and motivational saliency of drug-related cues, which contribute to the risk for relapse[11]. In addition, CBD appears to attenuate the reactivity to stressors among individuals with social anxiety disorder. Stress-reactivity is another important driver of relapse risk among OUD patients. However, no human studies have been conducted in individuals with OUD to examine the impact of CBD on neurocognitive deficits including stress reactivity. Therefore, the critical question this study aims to answer is whether CBD can reduce cue- and stress-reactivity, reduce attentional bias to drug-related cues, and improve decision making in individuals with OUD.

2. Specific Aims and Objectives

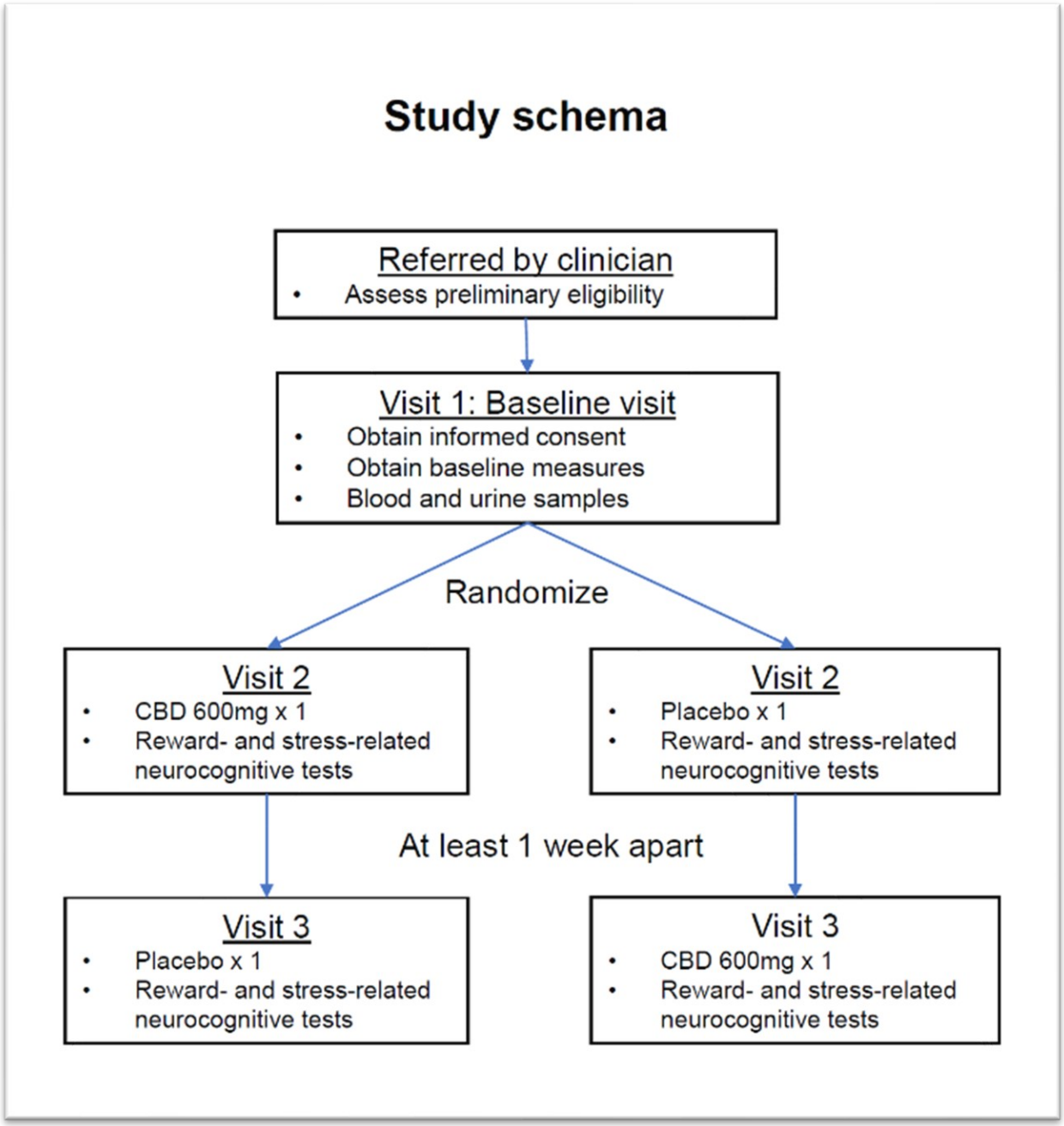
To evaluate the impact of CBD on cue- and stress-reactivity, decision making, and attentional bias in individuals with OUD currently in treatment with medications for OUD (MOUD).

- Approach: In a double-blind, placebo-controlled, cross-over trial, reward-related neurocognitive processes will be assessed after administration of CBD 600mg or placebo
- Primary Outcome: The primary outcomes is cue-induced cravings (Opioid Craving Scale).
- Secondary Outcomes: The secondary outcomes are impulsive decision making (Iowa Gambling Task, Monetary Choice Questionnaire), attentional bias (Visual Probe Task), and physiologic and subjective stress-reactivity.
- Hypothesis: Individuals with OUD in MOUD treatment taking CBD will demonstrate less cue-induced cravings, stress-reactivity, poor decision making, delayed discounting, attentional bias and stress reactivity than those receiving placebo

3. General Description of Study Design

Overall study design: Double-blind, placebo-controlled, cross-over trial

Study schema: Shown below.


Study schema
Referred by clinician
• Assess preliminary eligibility
Visit 1: Baseline visit
• Obtain informed consent
• Obtain baseline measures
• Blood and urine samples
Randomize
Visit 2
• CBD 600mg x 1
• Reward- and stress-related neurocognitive tests
Visit 2
• Placebo x 1
• Reward- and stress-related neurocognitive tests
At least 1 week apart
Visit 3
• Placebo x 1
• Reward- and stress-related neurocognitive tests
Visit 3
• CBD 600mg x 1
• Reward- and stress-related neurocognitive tests

4. Subject Selection

The proposed study is a double-blind, placebo-controlled, cross-over trial. The study will enroll 10 adult subjects with OUD currently receiving MOUD treatment with sublingual buprenorphine or methadone. Recruitment will occur from the outpatient programs that treat OUD patient at Brigham and Women's Hospital and Brigham and Women's Faulkner Hospital in Boston, MA, and at the Rutland Regional Medical Center in Rutland, Vermont.

Inclusion criteria:

- Age 18 to 65
- English speaking
- Receiving either buprenorphine or methadone for treatment of opioid use disorder for at least 3 consecutive months prior to enrollment
- Agreeable to abstaining from using any cannabis or CBD products for the duration of the trial.

Exclusion criteria:

- Any self-reported use of cannabis or CBD products in the past 30 days
- Current marijuana users
- Baseline depression (PHQ9) or anxiety (GAD7) scores of greater than 10
- Currently pregnant
- Hepatic liver enzymes greater than 3x upper normal limit
- Hypersensitivity to cannabinoids, sesame oil (CBD solution comes in sesame oil emulsion), or artificial strawberry flavoring.
- Currently taking any medications with known significant pharmacokinetic interactions with CBD

Subject recruitment procedures:

- We will use a variety of approaches to recruit for this study. We will use posted flyers at BWH clinical sites where OUD patients are being treated, and advertisements posted on Rally website. We will also utilize the Patient Gateway messages sent directly to active patients by sending an IRB-approved letter for recruitment. Potential participants will be identified by RPDR by searching for any MGB patient being treated with buprenorphine or methadone in their

medication list and also with a diagnosis of an opioid use disorder. In addition, research staff will approach clinical staff during the staff meetings.

- The RA will be largely responsible for identifying and recruiting potential participants.
- Individuals will be recruited as soon as IRB approval is obtained and will continue until target sample size (n=10) is reached or when project period ends on December 31, 2022.
- Individuals will be recruited from the Boston area, and patients being treated for OUD at BWH affiliated clinical programs.
- OUD is present in about 3% of Massachusetts residents, and we have over 500 active OUD patients across BWH affiliated clinical programs with OUD and therefore should be able to reach recruitment target.
- At our clinical sites, Black and Latino patients are over-represented, and therefore our study will likely recruit an ethnically and racially diverse participant population.

5. Subject Enrollment

Adults with a DSM-5 diagnosis of OUD and who are currently in treatment with buprenorphine or methadone will be recruited. Patients with OUD at Brigham and Women's Hospital (BWH) and Brigham and Women's Faulkner (BWF) will be referred to study staff by their health care providers at these clinical sites for possible inclusion. Their health care providers, who will be known to the potential subject and will have first-hand knowledge of the patient's medical history, will (1) first give approval for his/her patient to be contacted/approached for research purposes, (2) initially introduce the study to the patient, and (3) obtain the patient's permission, verbally during the course of providing medical care, to be contacted by study staff. Subjects will also be recruited from the Partners Clinical Trials website, http://Rally.partners.org, as well as print advertisements and flyers posted at the clinics. Study visits will be conducted at the BWH Center for Clinical Investigation. Study staff will perform a preliminary screen on the telephone or virtually to establish suitability for the study. If suitable, a study staff will schedule the individual for a baseline visit which will be performed remotely or in-person. Informed consent will be obtained at the baseline visit in-person or remotely, after which the full inclusion and exclusion criteria will be applied. For remote consenting, study staff will utilize the Mass General Brigham REDCap eConsent. Those who meet criteria will then be randomized to either CBD first or placebo first, and scheduled for the two study visits.

6. STUDY PROCEDURES

Overall approach: A total of 3 study visits are planned (**Table 1**) The first visit is the baseline visit, and the other two are double-blind placebo-controlled medication visits, where either CBD or placebo will be administered. Participants will be randomized using a random-number generator in a 1:1 ratio of CBD to placebo. During the baseline visit, after obtaining informed consent, participants will complete the baseline assessments. The subject will then be scheduled for their study visits 2 and 3 during which they will receive CBD or placebo in random order in double-blind fashion. Visits 2 and 3 will be scheduled at

least 1 week apart to function as a washout. Baseline visit will take no longer than an hour, and the subsequent visits will take no more than 2 hours to complete.

Visit 1: Baseline
Participants will provide written informed consent, obtained by the PI or another study physician. The blood and urine samples collected during the Baseline Visit will be used for inclusion/exclusion purposes. Specifically, participants who are currently pregnant (as confirmed by the pregnancy test), or have hepatic liver enzymes greater than three times the upper normal limit (as confirmed by the liver function tests, or LFTs) will be excluded. Subjects will also complete baseline PHQ9, GAD7, BPI, TLFB, COWS, PANAS, and opioid cravings.

Visit 2: CBD or placebo
After arrival to the study site, the participant will receive either the CBD 600mg or placebo, immediately followed by obtaining baseline heart rate, blood pressure, PHQ9, GAD, BPI, TLFB, COWS, opioid cravings, and urine sample for toxicology testing. Heart rate and blood pressure will be monitored every 30 minutes (vital signs: heart rate, blood pressure) following receipt of CBD or placebo. At 60 minutes following the CBD or placebo administration, the participant will then proceed to complete the cue-reactivity test, visual probe task, Iowa gambling task, monetary choice questionnaire (MCQ), and the mirror tracing persistence task (MTPT). Just prior to and after the MTPT task, subjects will provide salvia sample and complete the positive and negative affect scale (PANAS). An additional saliva sample will be collected 20 minutes after the MTPT task.

Visit 3: CBD or placebo
The same procedures for Visit 2 will be repeated during visit 3, scheduled at least 1 week after visit 2. The order in which CBD or placebo is administered will be randomized.

Cannabidiol:

Subjects will receive 600mg of oral CBD or matching placebo. Cannabidiol will be provided using Epidiolex™ oral solution 100mg/mL. Drug will be procured by the BWH Investigational Drug Services (IDS) pharmacy and the pharmacy at Rutland Regional Medical Center. The CBD or matching placebo will be placed in in oral syringes for the subjects to self-administer at the study site. CBD will be stored at room temperature (68 to 77 F) in its original bottle and in an upright position. Once opened, CBD has a shelf life of 84 days.

Study visit number	1	2	3
Informed consent	X		
Pregnancy test	X		
Liver Function Test	X		
Urine toxicology	X	X	X
Heart rate, blood pressure	X	X	X
PHQ9	X	X	X
GAD7	X	X	X
BPI	X	X	X
TLFB	X	X	X
COWS	X	X	X
PANAS	X	X	X
Opioid Cravings	X	X	X
Cue- and stress-reactivity		X	X
Visual Probe Task		X	X
Iowa Gambling Task		X	X
Monetary Choice Questionnaire		X	X
CBD 600mg or Placebo		X	X
Adverse effects		X	X

Table 1: Schedule of assessments
PHQ-9=Patient Health Questionnaire; GAD7=Generalized Anxiety Disorder 7; BPI=Brief Pain Inventory; TLFB=Time-Line Follow Back; COWS=Clinical Opioid Withdrawal Scale; PANAS=Positive and Negative Affect Schedule

Primary Outcome: The primary outcomes is the change in cue-induced cravings (Opioid Craving Scale).

Secondary Outcomes: The secondary outcomes are impulsive decision making (Iowa Gambling Task, Monetary Choice Questionnaire), attentional bias (Visual Probe Task), and physiologic and subjective stress-reactivity.

Assessments:

- Patient Health Questionnaire 9-item (PHQ9): Assessment of depressive symptoms
- Generalized Anxiety Disorder 7-item (GAD7): Assessment of anxiety symptoms
- Brief Pain Inventory (BPI): Pain severity and interference assessment.
- Time-line follow back (TLFB): A method of assessing for recent substance use using a calendar.
- Clinical Opioid Withdrawal Scale (COWS): Assessment of opioid withdrawal.
- Opioid craving scale[12]: A 3-item tool to assess current cravings, cravings when exposed to triggers, and likelihood of using if placed in an environment that the individual previous used opioids.
- Cue-induced craving[13]: Participants will be shown both illicit opioid-related and neutral images on a computer screen for one minute each using a standardized protocol. The order in which the cues will be presented will be randomized and counter balanced. Participants will rate their cravings on a visual analog scale. The cue exposure procedure will end with a standardized debriefing exercise. It is important to note that cue-exposure is a safe paradigm for studying craving in this population when employing debriefing procedures.
- Monetary Choice Questionnaire (MCQ)[14]: This is a 27-item self-report tool used to measure delayed discounting, or the degree to which individuals prefer smaller immediate rewards compared to larger delayed rewards. Participant are asked to choose between a smaller (in dollars) immediate reward and a larger delayed reward.

- Iowa Gambling Task (IGT)[15]: This is a task to measure decision making, which utilizes four decks of cards (A, B, C, D). Participants are instructed to maximize profits by selecting cards from any deck. Cards from decks A and B earn more profits but lead to even higher occasional losses leading to net long-term losses, while decks C and D yield low profits but only low occasional losses resulting in a net long-term profit.
- Visual Probe Task[16]: Opioid-related and neutral images will be used. Each trial will begin with a fixation point lasting 500ms. A pair of images then will appear on the left and right of the screen for either a short (200ms) or long (500ms) stimulus duration to assess automatic orientating and controlled attention processing, respectively. Image pairs will be replaced by a probe in the location of either the opioid-related or neutral image. The probe will remain until the participant responds to identify the probe orientation by pressing the response keys as quickly as possible.
- Mirror Tracing Persistence Task (MTPT)[17,18]: This task functions to elicit a stress response and measures distress tolerance. Participants are asked to trace a red dot along the lines of a geometric shape (e.g., star) using the computer's mouse, but the mouse moves the red dot in the reverse direction. Each time the participant moves the mouse out of the lines or hesitates for more than 2 seconds, a buzzer sounds, and the dot moves back to the beginning. Three progressively more difficult shapes are used. The first two rounds last 1 minute each. The third and final round tests for distress tolerance. Participants may terminate the task at any point during the third round by pressing on the space bar. In addition to measuring distress tolerance, prior studies have shown consistently that this method elicits a robust stress response in individuals with substance use disorders.
- Positive and Negative Affect Schedule (PANAS): Subjective stress reactivity will be measured using the Negative Affect subscale of the PANAS, a routinely used measure of both positive and negative emotions. This will be administered before and after stress induction with MTPT.
- Salivary cortisol: Hypothalamic-pituitary-adrenal (HPA)-axis response will be measured by collecting saliva for analysis of salivary cortisol before, immediately after, and 20-minutes after the stressor task.

Compensation: Participants will be reimbursed for travel/parking. In addition, subjects will be compensated $100 for completing the baseline visit, $50 for visit 2 and $100 for completing visit 3 ($250 total for completing all visits). We will utilize the Advarra payment systems to provide the study compensation.

Stopping rules: The Principal Investigator will assess all patients with regard to stopping criteria. This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

Data sharing: Data collected will be shared by investigators at BWH as well as with investigators at Rutland Regional Medical Center using MGB Dropbox Business. Regarding sharing of data with the study sponsor, the principal investigator will be required to provide regular written progress reports. No identifiable information will be shared with the sponsor. Data collected at Rutland Regional Medical Center will only be kept for record-keeping requirements, and will not be used for future studies not described in this protocol. If the participant wished to withdraw their data from then we will withdraw the participant from the study as outlined in the protocol. Subjects who wish to withdrawal their data can ask the PI to do so. We are concurrently seeking IRB approval from Rutland Regional Medical Center.

7. Risks and Discomforts

The well-being of the study participants is of utmost importance. The in-depth screening procedure has been designed to ensure that individuals with any underlying medical or psychiatric illness are identified that may place them at greater risk for experiencing adverse effects during the study. The protocol raises several areas of concerns: confidentiality, emotional distress, adverse reactions to study procedures, suicidal ideation, and cannabidiol medication.

Confidentiality: Confidentiality is of utmost importance given the sensitive nature of the illness and data collected. During research there is always a possibility for a breach of confidentiality, which may potentially cause personal, social, occupational, legal, and other harm. Our research team is very aware of the importance of maintaining strict confidentiality and has prior experience dealing with sensitive information. The following precautions will be used to protect the privacy of participants and maintain confidentiality of research data: all staff will be trained in confidentiality and data security procedures; privacy will be maintained by conducting all study procedures in private hospital rooms or in close, sound-proof rooms; data will be de-identified and coded with unique ID numbers; data will be securely stored in locked filing cabinets in locked rooms; electronic data will be stored in password protected documents located on password protected computers and secure servers; the key linking participants names and ID numbers will be stored in a separate password protected document in a password protected computer; access to data storage areas will be restricted to authorized study personnel; and all analysis will be conducted on de-identified data. While breach of confidentiality is possible, these safeguards will ensure that such a breach will be highly unlikely.

Emotional distress: Some patients may experience discomfort or embarrassment related to providing urine samples or answering questions about substance use and other personal behaviors. They could also experience unexpected encounters with friends or associates while in the study. However, based on prior studies with this population, we expect the degree of distress to be very limited. All research personnel will be extensively trained on study procedures, including the conduct of the interviews that elicit personal information, and the importance of being sensitive to and respectful of all participants. In cases where emotional distress does occur, research personnel will be trained on how to identify and address it, and when to terminate an interview. Multiple levels of back-up support for research personnel will be

developed. The candidate is a board certified psychiatrist, and will be able to ensure that appropriate services are received.

Adverse reactions to study procedures: The study procedures will end with a standardized relaxation and debriefing exercise. Before participants are discharged from each study session, their well-being will be assessed by the study staff and a standardized safety and adverse events questionnaire will be used to assess any adverse events. If needed, participants will be referred for further clinical evaluation and assistance. It is important to note that cue-exposure and stress-exposure are safe paradigms for studying this patient population when employing debriefing procedures.

Suicidal ideation: Patients with OUD frequently have psychiatric co-morbidities, namely depression. Participants who disclose any suicidal ideation during the study (either through spontaneous expression of suicidal ideation, or self-reported on the PHQ-9) will result in emergent evaluation by a licensed clinician member of the study staff for appropriate assessment and triage. Any disclosures will be handled within existing legal mandates, clinical practice, and social norms. Consistent with standard clinical practice, when possible, disclosures will be discussed with the participant to determine the best management options. This may include notifying the outpatient providers or family members, referring to medical treatment, calling emergency services, or escorting the participant to the Emergency Room at Brigham and Women's Hospital. When required by law, the police department will be notified. The candidate is a board certified psychiatrist and has extensive experience managing acutely distressed patients with mental or substance use disorders.

Cannabidiol medication safety: All subjects in this trial will receive a single dose of 600mg of cannabidiol. Cannabidiol (Epidiolex) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of seizures associated with two rare and severe forms of epilepsy. However, cannabidiol is not approved by the FDA for treatment of opioid use disorder. The PI has conducted a previous pilot trial of CBD 600mg administered to OUD patients for 3 consecutive days in a single-arm open-label design. That protocol was reviewed by the Center for Drug Evaluation and Research at the Food and Drug Administration and determined it met the regulatory criteria for an exemption from the requirement for the Investigational New Drug (IND) submission, and we therefore received the FDA IND exemption letter November 13, 2019. This protocol uses the same medication (Epidiolex), at the same dose (600mg), for the same patient population (OUD on buprenorphine or methadone), and will administer for only one dose instead of three consecutive days. As such, we feel an additional FDA IND is not required to conduct this trial. Although this proposed clinical evaluation is for an "off-label" indication of cannabidiol, it does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the Epidiolex (cannabidiol). The proposed dose is within FDA-approved mg/kg maximum daily dose limits. There are now two randomized placebo-controlled studies of administering 400mg or 800mg of cannabidiol to participants with opioid use disorder with no adverse effects. Nonetheless, cannabidiol may cause participants to experience side effects such as: somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; infections; and suicidal thoughts or actions. All participants will be told of these potential side effects, and the screening procedures, including liver function tests, are in place to minimize these

potential risks. The principal investigator will continually assess and monitor adverse effects both during and after cannabidiol administration, as noted in the Schedule of

8. Benefits

No benefits can be guaranteed from participation in the study. However, all enrolled participants will be receiving an adjunctive agent that is hypothesized to help reduce cue-induced cravings associated with their opioid use disorder, and it is possible that at least some subjects will experience a decrease in the severity of their cravings or stress-reactivity. An extensive screening procedure will ensure that individuals entering the trial will have no contraindications. Trained research personnel will perform all study procedures to minimize risks, discomforts, and adverse effects. Buprenorphine and methadone treatment are FDA-approved treatment for the treatment of OUD, and reduces illicit opioid use and related morbidities associated with OUD. This study will generate valuable information about the effect of combining cannabidiol with stable doses of buprenorphine or methadone for patients with OUD. The results will help inform the direction needed to take in developing effective strategies to improve the care of OUD patients taking medications. If successful, this line of research has the potential to significantly impact clinical practice of treating OUD by providing a viable medication adjunct to existing evidenced-based therapies.

9. Statistical Analysis

For all analyses, descriptive statistics will be used to summarize the data. All comparisons will utilize paired t-tests or non-parametric tests where appropriate. Alpha will be set at 0.05 for all analyses.

Primary outcome:

- Cue-reactivity: Cue-reactivity will be defined as the difference between baseline craving scores and the craving scores in response to opioid-related or neutral cues.

Secondary outcome:

- Subjective cravings: Craving scores will be rated on a 0 to 10 visual analog scale for each of the 3 items.
- Attentional bias: This is calculated as the difference in reaction time (RT) between when the probe replaced the neutral compared with the opioid-related images (i.e. RTneutral – RTopioid).
- Delayed discounting: Based on their responses to the MCQ, the rate of discounting, or k value, is calculated, which range from 0.00016 to 0.25. Higher values indicate greater discounting and impulsivity.
- Impulsive decision making: A net score from the IGT is calculated by subtracting the number of disadvantageous selections from the number of advantageous selections (i.e. (C+D) - (A+B)), where negative scores indicate decision-making that favors immediate rewards despite negative consequences.

- Distress tolerance: This is measured as the length of time in number of seconds that participants engage in the third MTPT task.
- Subjective stress reactivity: Subjective stress reactivity will be calculated as the difference in the negative affect score from PANAS before and after the stressor task.
- Physiologic stress reactivity: Physiologic stress reactivity will be calculated as the difference in salivary cortisol levels and skin conductance before and after the stressor task.

Power analysis: The estimated mean change in cue-induced cravings scores from prior studies is -1.5 (SD 1.5). Based on this estimate, and a conservative estimate of a correlation of r=0.60 between the two time points, a sample size of 10 is needed for 88% power and two-tailed alpha set at 0.05 for a paired-samples t-test. A point estimate of the difference in the change and the 95% confidence interval will be reported. Conversely, if the change in cravings is not normally distributed, then a sum rank test will be used.

10. Monitoring and Quality Assurance

INSTRUCTIONS
Delete grey Instructions box upon completion of this section

Describe the plans that will be followed by study staff for monitoring and quality assurance, including:

- Adverse event criteria and reporting procedures
- Planned safety monitoring, e.g., data monitoring committee (DMC)/data and safety monitoring board (DSMB), independent monitor, PI-monitored, etc., including planned frequency of review. If DMC/DSMB monitored, include either charter as separate attachment or complete DMC/DSMB APPENDIX
- Outcomes monitoring, including planned frequency of review.
- Study stopping rules as applicable
- Internal monitoring of source data, protocol adherence, and recordkeeping, including which staff will be responsible and planned frequency of review
- Independent monitoring of source data as applicable

The Principal Investigator, Dr. Joji Suzuki, will be responsible for monitoring the safety of all subjects. The PI or study staff will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol on a regular basis (i.e. weekly). Study staff are located at Brigham and Women's Hospital in Boston, MA, and Rutland Regional Medical Center in Rutland, Vermont. Study safety meetings, including the principal investigator, study coordinators, and study physicians will occur weekly to review the progress of currently-enrolled subjects and any reported side effects.

Data collected will be shared by investigators at BWH as well as with investigators at Rutland Regional Medical Center using MGB Dropbox Business. Regarding sharing of data with the study sponsor, the principal investigator will be required to provide regular written progress reports. No identifiable information will be shared with the sponsor.

Data collected at Rutland Regional Medical Center will only be kept for record-keeping requirements, and will not be used for future studies not described in this protocol. If the participant wished to withdraw their data from then we will withdraw the participant from the study as outlined in the protocol. Subjects who wish to withdrawal their data can ask the PI to do so. We are concurrently seeking IRB approval from Rutland Regional Medical Center.

The Principal Investigator will assess all patients with regard to stopping criteria. This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☐ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

Confidentiality is of utmost importance given the sensitive nature of the illness and data collected. During research there is always a possibility for a breach of confidentiality, which may potentially cause personal, social, occupational, legal, and other harm. Our research team is very aware of the importance of maintaining strict confidentiality and has prior experience dealing with sensitive information. The following precautions will be used to protect the privacy of participants and maintain confidentiality of research data: all staff will be trained in confidentiality and data security procedures; privacy will be maintained by conducting all study procedures in private hospital rooms or in close, sound-proof rooms; data will be de-identified and coded with unique ID numbers; data will be securely stored in locked filing cabinets in locked rooms; electronic data will be stored in password protected documents located on password protected computers and secure servers; the key linking participants names and ID numbers will be stored in a separate password protected document in a password protected computer; access to data storage areas will be restricted to authorized study personnel; and all analysis will be conducted on de-identified data. While breach of confidentiality is possible, these safeguards will ensure that such a breach will be highly unlikely.

12. References

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APPENDIX A

Data Monitoring Committee / Data and Safety Monitoring Board Appendix

- *To be completed for studies monitored by Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) if a full DMC/DSMB charter is not available at the time of initial IRB review.*
- *DMC/DSMB Charter and/or Roster can be submitted to the IRB later via Amendment, though these are not required.*

A Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) will be convened for safety monitoring of this research study. The following characteristics describe the DMC/DSMB convened for this study (Check all that apply):

☐ The DMC/DSMB is independent from the study team and study sponsor.

☐ A process has been implemented to ensure absence of conflicts of interest by DMC/DSMB members.

☐ The DMC/DSMB has the authority to intervene on study progress in the event of safety concerns, e.g., to suspend or terminate a study if new safety concerns have been identified or need to be investigated.

☒ Describe number and types of (i.e., qualifications of) members:
The PI will serve as the data monitor given the small size of the study and low risk associated the use of a single dose of CBD. Given that this study will enroll a total of 10 subjects to receive a single dose of CBD 600mg or placebo, that study end points are not serious events (i.e. cue-reactivity), the risks associated with CBD is low, and that the study is completed rather quickly, the PI will serve as the data monitor. The PI will promptly report any adverse events to the IRB and the FDA where appropriate.

☐ Describe planned frequency of meetings:
Click or tap here to enter text.

☐ DMC/DSMB reports with no findings (i.e., "continue without modifications") will be submitted to the IRB at the time of Continuing Review.

☐ DMC/DSMB reports with findings/modifications required will be submitted promptly (within 5 business days/7 calendar days of becoming aware) to the IRB as an Other Event.

Protocol Title: Cannabidiol on reward-and stress-related neurocognitive processes in individuals with opioid use disorder: A double-blind, placebo-controlled, cross-over trial

Principal Investigator: Joji Suzuki, MD

Site Principal Investigator:

Description of Subject Population: Patients with opioid use disorder who are receiving buprenorphine or methadone treatment

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 Mass General Brigham 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?

We are doing this research study to find out if using cannabidiol (CBD, also known as Epidiolex) along with buprenorphine or methadone can help patients with opioid use disorder by reducing their cravings and stress.

How long will you take part in this research study?

If you decide to join the research study, it will take you about 2 weeks to complete the study. During this time, we will ask you to make three study visits to Brigham and Women's Hospital in Boston, MA.

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

The study requires 3 visits over the course of 2 weeks to the Clinical Trials Hub at Brigham and Women's Hospital. Each visit lasts between approximately 45 minutes to 2 hours. In the first study visit, we will ask you about your psychiatric and medical history, obtaining your blood and urine sample, as well as asking about your mood and cravings. In the second visit, you will receive either cannabidiol or placebo. Neither you or the study staff will know if you are receiving cannabidiol or placebo. After that, we will be using a computerized assessment tool to conduct several psychological tests to measure how your brain reacts. On the third visit, you will receive cannabidiol or placebo, and repeat the same assessments. You will receive both cannabidiol and placebo, but the order will be randomized so that if you receive cannabidiol in the second visit, you will receive placebo in the third visit. If you receive placebo on the second visit, you will receive cannabidiol on the third visit.

Why might you choose to take part in this study?

We cannot promise any benefits to you from taking part in this research study. However, possible benefits may include a reduction in cravings and stress related to your opioid use disorder**.** Others with opioid use disorder may benefit in the future from what we learn in this study.

Why might you choose NOT to take part in this study?

Taking part in this research study has some risks and requirements that you should consider carefully.

Important risks and possible discomforts to know about include possibility for a breach of confidentiality, and experiencing emotional distress related to answering questions about substance use and other personal behaviors.

A detailed description of side effects, risks, and possible discomforts can be found later in this consent form in the section called "What are the risks and possible discomforts from being in this research study?"

What other treatments or procedures are available for your condition?

You do not have to take part in this research study to be treated for substance use disorder. Other treatments or procedures that are available to treat substance use disorder include:

- Individual psychotherapy or group therapy
- Peer recovery services, like Narcotics Anonymous (NA)

Talk with the study doctor if you have questions about any of these treatments.

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.
Joji Suzuki, MD is in charge of this research study. You can call him if you have questions about the study, scheduling of appointments or study visits at 617-732-5752 between M-F 9am-5pm.

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

Detailed Information

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Why is this research study being done?

We are doing this research study to find out if using cannabidiol (CBD) along with buprenorphine or methadone can help patients with their opioid use disorder. You will not receive buprenorphine or methadone as a part of this research study; in order to be able to take part in this study you must already be receiving buprenorphine or methadone as part of your standard clinical care.

Cannabidiol is a non-psychoactive and non-addictive constituent in cannabis. Cannabidiol is approved by the U.S. Food and Drug Administration (FDA) for the treatment of seizures associated with two rare and severe forms of epilepsy. However, cannabidiol is not approved by the FDA to treat opioid use disorder.

This research will compare cannabidiol to placebo. The placebo looks exactly like cannabidiol but contains no cannabidiol. During the study you may get a placebo instead of cannabidiol. Placebos are used in research studies to see if the results are due to the study drug or other reasons. At some time during the study, we will give you cannabidiol. At another time, we will give you placebo.

Who will take part in this research?

We are asking you to take part in this research study because you have a diagnosis of opioid use disorder, and you have been receiving a stable dose of buprenorphine or methadone treatment. Opioid use disorder is defined as a problematic pattern of opioid use that leads to serious impairment or distress. Doctors use a specific set of criteria to determine if a person has a substance use problem.

About 20 subjects will take part in this research study. About 5 subjects will complete the research study at Brigham and Women's Hospital (BWH) in Boston MA.

The President and Fellows of Harvard College, a non-profit organization, is paying for this research to be done.

What will happen in this research study?

At the beginning of the study we will ask you questions to see if you are eligible to take part in the study. If you are deemed eligible to proceed with the study, we will ask you to sign this consent form before we do any study procedures.

Screening and Baseline Visit (Visit 1)

The Screening and Baseline Visit will take about 45 minutes. At this visit, we will ask you a number of questions and do some tests to see if you qualify to take part in this research study. The study doctor will review the results of these tests and procedures. If you don't qualify, the study doctor will tell you why.

At this visit, we will:

- Ask you about your medical history, including questions about mental health
- Ask you to fill out some questionnaires about your mental and emotional health, physical symptoms, and your general health and well-being
- Ask you about medications you are taking
- Draw a blood sample
- Ask you for a urine sample
- Test your urine for certain drugs
- Test your urine for pregnancy, if you are a female able to become pregnant. Pregnant women cannot take part in this research study.
- Monitor your vital signs (blood pressure, heart rate)

Urine Drug Screen

During this study, we will test your urine for certain drugs, including cannabis and illegal drugs like cocaine. The results of the urine drug test will not become part of your medical record. These test results will, however, remain part of your study record.

Study Visit 2: CBD or placebo

Visit 2 will take about 2 hours to complete. At this visit we will:

- Have you take your first dose of cannabidiol or placebo. You nor the study staff will know which one you are taking, but you will eventually take both in the course of the study.
- Ask you about your cravings for opioids, mood, anxiety, pain, and the use of any alcohol or drugs in the past week.
- Ask you to complete 5 psychological tests to test your cravings in response to seeing images related to drugs, two tests on decision making, attention to drug-related images, and your response to a stressor. These tests will all be administered by a computer.
- Ask you to provide 3 saliva samples during the psychological tests.
- Ask you to complete a debriefing exercises

Study Visit 3: CBD or placebo

Visit 3 will take about 2 hours to complete. The exact same procedure will be followed during this visit as compared to the previous, except the drug that you will receive. At this visit we will:

- Have you take your second dose of cannabidiol or placebo. You nor the study staff will know which one you are taking, but you will have taken both in the course of the study.
- Ask you about your cravings for opioids, mood, anxiety, pain, and the use of any alcohol or drugs in the past week.
- Ask you to complete 5 psychological tests to test your cravings in response to seeing images related to drugs, two tests on decision making, attention to drug-related images, and your response to a stressor. These tests will all be administered by a computer.
- Ask you to provide 3 saliva samples during the psychological tests.
- Ask you to complete a debriefing exercises

Also, the study doctor may take you out of the study without your permission. This may happen because:

- The study doctor thinks it is best for you to stop taking the study drug
- You develop a condition (such as suicidal thoughts) that needs emergency care
- You can't make the required study visits
- The Sponsor decides to stop the study
- We stop doing the study for other reasons

If this happens, the study doctor will explain why you need to stop taking part in the study. We will ask you to come in for a final study visit as described above.

Study Information Included in Your Electronic Medical Record

A notation that you are taking part in this research study may be made in your electronic medical record. Information form the research that relates to your general medical care may be included in the record (for example: lists f allergies, results of standard blood tests done at the hospital labs).

Please ask your study doctor if you have any questions about what information will be included in your electronic medical record.

Sending study information to research collaborators outside Mass General Brigham

We will send your study information and/or samples to researchers working with us at Rutland Regional Medical Center. We will label all your study materials with a code instead of your name. The key to the code connects your name to your study information and samples. We will keep the key to the code her at Mass General Brigham and will not share it with our research collaborators. No one outside of Mass General Brigham will know which study information or samples are yours.

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

The information we collect in this study may help advance other research. If you join this study, we may 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. Information and/or samples may be shared with investigators at our hospitals, at other academic institutions or at for-profit, commercial entities. You will not be asked to provide additional informed consent for these uses.

Will you get the results of this research study?

You and your doctor should not expect to get information about the results of the research study or the results of your individual participation in the research study. We will study samples and information from many people. It could take many years before anyone knows whether the results have any meaning. There is a small chance that we could find out something from the study that might be important to your health. If this happens, we may contact you to find out if you would like to learn more. However, even if we find something important to your health, we cannot guarantee that you will be contacted.

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

Risks of Taking Cannabidiol

Taking cannabidiol may cause you to have one or more of the side effects listed below.

Common side effects:

- Sleepiness
- Decreased appetite
- Diarrhea
- Increase in liver enzymes
- Feeling very tired and weak
- Rash
- Sleep problems
- Infections

Less common side effects:

- Suicidal thoughts or actions (about 1 in 500)

There may be other risks of cannabidiol that are currently unknown.

Cannabidiol may cause liver problems. Call the study doctor right away if you develop any of these signs and symptoms of liver problems during treatment with cannabidiol:

- loss of appetite, nausea, vomiting; fever
- feeling unwell, unusual tiredness
- yellowing of the skin or the whites of the eyes (jaundice)
- itching
- unusual darkening of the urine
- right upper stomach area pain or discomfort

Cannabidiol may cause you to feel sleepy, which may get better over time. Other medicines (e.g. clobazam) or alcohol may increase sleepiness. Do not drive, operate heavy machinery, or do other dangerous activities until you know how cannabidiol affects you.

Like other antiepileptic drugs, cannabidiol may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. Call the study doctor right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempt to commit suicide
- new or worsening depression
- new or worsening anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worsening irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.

Risks to an Embryo or Fetus, or to a Breastfeeding Infant

The effect of cannabidiol on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant
- Trying to become pregnant
- Breastfeeding

If you are a menopausal woman and have not had a menstrual period for the past 12 months or more, you will not need to have a pregnancy test. Also, if you have had any well-documented method of surgical sterilization, you will not need to have a pregnancy test. Methods of surgical sterilization include having had a hysterectomy (removal of the uterus), bilateral oophorectomy (removal of both ovaries), a tubal ligation (having your tubes tied), and transvaginal occlusion (plugging the opening of the tubes with a coil). All other female subjects must have a negative pregnancy test before starting the study drug.

If you are sexually active and able to become pregnant, you must agree to use one of the birth control methods listed below. You must use birth control for the entire study and for at least one (1) month after your last dose of study drug.

Acceptable birth control methods for use in this study are:

- hormonal methods, such as birth control pills, patches, injections, vaginal rings, or implants
- barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- intrauterine device (IUD)
- abstinence (no sex)

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you must stop taking the study drug and stop taking part in the study.

Risks of Taking Cannabidiol with Other Medications

Do not take valproate, clobazam, theophylline, caffeine, alcohol, bupropion, efavirenz, diflunisal, propofol, fenofibrate, gemfibrozil, lamotrigine, morphine, lorazepam, phenytoin, or diazepam while you are in the study. Taking these drugs and cannabidiol together may cause serious side effects.

For your safety during this study, call your study doctor BEFORE you take any:

- new medications prescribed by your own doctor
- other medications sold over-the-counter without a prescription
- dietary or herbal supplements

Only a small number of people have taken cannabidiol. Therefore, we don't know about all the side effects that can happen when taking cannabidiol with other drugs.

Risks of Blood Draws

You may have a bruise (a black and blue mark) or pain where we take the blood samples. There is also a small risk of infection, lightheadedness, and/or fainting.

Risks of Gathering Sensitive Information

Some people may find answering questions about their emotional state and substance use or other personal behaviors upsetting. Although safeguards are put in place to protect your privacy, it is possible that a breach in confidentiality could occur. In that event, there is a risk of confidential sensitive information being accessible by others. This could be emotionally distressing.

Risks Regarding the Psychological tests

As described above, we will be using a computerized psychological tests to see how cannabidiol affects your cravings, decision making, attention to drugs, and reaction to stressors. Some of these tests will show you images that might resemble situational or environmental triggers in your life that could typically cause you to crave opioids. There is a possibility that you could experience mild to moderate opioid cravings in response to the images shown in the cue-reactivity testing. This could be emotionally distressing. There are measures in place to assess your well-being after the procedure, including a standard relaxation and debriefing exercise. If needed, you will be referred for further clinical evaluation and assistance.

If we learn information from you during this study that indicates an intent to seriously harm others or yourself, we may be required by law to share that information with third parties, including public safety or law enforcement authorities, and may take other precautions to protect against such harm.

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

You may not benefit from taking part in this research. Others with opioid use disorder may benefit in the future from what we learn in this study.

What other treatments or procedures are available for your condition?

You do not have to take part in this research study to be treated for substance use disorder. Other treatments or procedures that are available to treat substance use disorder include:

- individual psychotherapy or group therapy
- peer recovery services, like Narcotics Anonymous (NA)

Talk with the study doctor if you have questions about any of these treatments.

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?

We will pay you $100 for completing the baseline visit, $50 for completing the second visit, and then $100 for completing the third visit.

We may be using an approved outside vendor (Advarra Technology Solutions) to make these payments to you via a reloadable credit card-based system, called Advarra Participants Payments. This secure system is similar to a gift card or credit card.

If you are paid by this system, you will be given a Participants Payments Visa card when you enroll in the study. Once the card is activated, the study team will add a payment after each paid visit you complete. The payment should be available to you within a day. You may use the card anywhere Visa cards are accepted, such as at a grocery store.

We will need to collect your Social Security Number in order to make these payments, and it will be shared securely with the company that runs the card-based system. Payments like this are considered taxable income. If you receive more than $600, the payment will be reported to the IRS as income by the hospital.

If you provide a receipt for something like travel expenses and we can cover that, that is not considered taxable income. Reimbursement of expenses will not be made using the Participant Payments card.

We will pay for parking in the hospital garage during study visits if you require parking.

We will pay for the cost of your public transportation (MBTA) up to $30 total, and/or parking in the hospital garage up to $30 total.

What will you have to pay for if you take part in this research study?

The President and Fellows of Harvard College, a non-profit organization is providing the funding to purchase the cannabidiol at no cost to you.

Study funds will pay for all study-related procedures and study visits that are done only for research.

We may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and copayments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs.

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

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

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.

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)

Statistical Analysis Plan

Descriptive statistics were used to summarize the data. The differences in heart rate, systolic blood pressure, and diastolic blood pressure recordings at 60 minutes post-dosing of CBD or placebo and at baseline values were compared. Cue-induced craving was calculated as the difference in post-cue craving scores in response to drug-related cues minus pre-cue craving scores. Attentional bias was calculated as the difference in reaction time to neutral cues and drug-related cues among drug-neutral trials with a correct response, such that positive scores indicated attentional bias towards drug-related cues. Scores from the IGT was calculated as the sum of the numbers selected from decks C and D, minus the number of cards selected from decks A and B. Delayed discount was calculated using a standardized conversion from the MCQ. Distress tolerance was measured as the number of seconds that participants persisted in the third trial of the MPTP. Paired t-test were used in all analyses, with alpha set at 0.05.