Title: Repeated Cannabis Administration on Experimental Pain and Abuse Liability

NCT: 04576507

Document date: April 14, 2025

IRB Approval date: February 10, 2025

Office of Mental Health

View xForm - IRB Protocol Form

Use this form to detail study procedures.

Data Entry

Study Basics

If you are a user with a dual role of IRB Member and PI (for your own research), there are two options when using the "Add a Note" feature:

- selection of "Internal Only" (display note to IRB Members and Administrative Staff only)--**Use when acting as a Board Member**
- deselection of "Internal Only" (display note to study team)--**Use when acting as a PI**

Submitter

Samantha Chong, BA

Email: Samantha.Chong@nyspi.columbia.edu **Business:** (646) 774-6108

Indicate whether you are an OMH research team submitting to the NKI IRB as part of your regular submission process (i.e., NKI IRB is your designated IRB of Record), or a NYSPI team submitting to the NKI IRB.

If you are an investigator from an OMH Psychiatric Center, you should select "OMH for NKI Review".

If you are a NYSPI investigator applying for NYSPI IRB review, please select "NYSPI for NYSPI Review (Determination request only (i.e NR and NHSR).

If you have questions regarding which designation is correct, please contact the NKI IRB at 845-398-2199, nki-irb@nki.rfmh.org

NYSPI for NKI Review

Transfer Type

☐ Transfer
☑ Transfer with Modifications
☐ Not a Transfer

Submission Type

If you are transferring data you must select "Modification Form" for the Submission Type below.

If you are trying to submit a request for determination of research select "New Study Application".

*If you are selecting "Personnel Changes ONLY Modification Form", this is **only used for** addition of OMH/OPWDD/NYSPI affiliated personnel, and removal of personnel with ANY affiliation.*

☑ Modification Form
☐ New Study Application
☐ Personnel Changes ONLY Modification Form

Main Location Output

NYSPI - New York State Psychiatric Institute

Is this a Modification to Restart? (i.e., are you submitting your letter signed by the IO to lift the Pause on your study?)

No answer provided.

IMPORTANT INFORMATION FOR STUDY TRANSFERS:

You have selected that this is either a "transfer", or "transfer with modifications". In the following sections, you will be asked to update the study PI (on this page) and all personnel associated with your study (on the next page).

The Personnel section should indicate all personnel that are currently approved and listed in your IRBNet personnel form. You will need to add each currently approved person to the table below and indicate their role on the study team.

If you selected "transfer" and wish to either add or remove personnel to your currently approved study, please go back and select "transfer with modifications". If you have selected "transfer with modifications" you will be able to add new personnel or remove personnel from your approved study in addition to any other changes you may wish to include.

Current Principal Investigator

Caroline Arout, PhD

Expirations:	Good Clinical Practice - 01/08/2125 • NKI and NYSPI GCP Training - 01/08/2125 • NKI and NYSPI IRB Training - 07/06/2026	**CV/Resume:**	Yes

Principal Investigator

Please type the Principal Investigator's name or email address.

*If there is no result for the contact you are attempting to add, submit a **New Contact Form** to add this person to the system.*

Caroline Arout, PhD

Email:	caroline.arout@nyspi.columbia.edu	**Phone:**	

CV/Resume on file:
Yes

Is the PI a Student Researcher?
No

Is the PI an OMH/RFMH/OPWDD Employee?
Yes

Is this modification related to a change in PI?
No

Study Coordinator (if applicable)

Individuals should be listed here who are not part of study personnel but are responsible for coordinating study documents within the OneAegis System. If this does not apply leave blank.

No answer provided.

Title of Project

Effects of Repeated High-Cannabidiol Cannabis Administration on Experimental Pain and Abuse Liability in Humans

Form Identifier

Modification Form - Caroline Arout, PhD

IRB Number

8016

This document is required for all research conducted at, or by researchers affiliated with, the Office of Mental Health for which the Nathan Kline Institute reviews research. If your study is a sponsored protocol, some of these sections may be detailed in the protocol provided by your sponsor. Please submit a copy of the Sponsor's Protocol. In this document you may provide the page number, version date, and the version number of the Sponsor's Protocol that is being referenced.

Modification Description

List Requested Changes

This information will be displayed in your approval letter. Please be concise.

Multiple updates are being made in this form to supplement the original approved protocol for clarity and completeness.

Please provide a justification for each change.

The original protocol was missing some of the elements required by the Nathan Kline Institute IRB. This form includes the updates to supplement the overall transfer of the study, which will be reviewed along with the Continuing Review lifecycle action, so that the study may be reviewed as a new submission to the new IRB of Record (NKI).

Does any change increase the risk to study subjects?

No

Please indicate the current study status.

☐ Enrollment Open; Study Procedures Ongoing
☐ Enrollment Closed; Study Procedures Ongoing
☐ Study Open for Long-Term Follow-up Only
☑ Study Open for Data Analysis Only

Do any of the changes require updates to the consent document or the consent process?

No

List the documents included with this modification to request this change:

1. Continuing Review coversheet

Study Personnel

Current Study Personnel

Name	Role	NKI and NYSPI GCP Training	NKI and NYSPI IRB Training
Alexis Marshall,	Research Assistant	06/20/2123	06/20/2026
Caroline Alleyne,	Research Assistant	07/10/2123	12/15/2026
Caroline Arout, PhD	Co-PI	01/08/2125	07/06/2026
Caroline Arout, PhD	Principal Investigator	01/08/2125	07/06/2026
Eric Parmon, MD	Co-Investigator	06/12/2122	06/12/2025
Felipe Castillo, MD	Co-Investigator	11/15/2124	01/29/2028
Jeanne Manubay, MD	Co-Investigator	07/14/2123	08/13/2025
Margaret Haney, PhD	Co-Investigator	01/09/2125	01/10/2028
Richard Foltin, PhD	Co-Investigator	12/12/2122	08/26/2027
Stephanie Reed, Ph.D.	Co-Investigator	11/09/2124	11/09/2027

Personnel do not need to be listed here if <u>all</u> of the following conditions are met:

- **They do not have access to any identifiers**
- **They do not consent or interact with subjects**
- **They are not listed on the Study Grant**

For more information, please refer to the NKI Personnel Policy.

Anyone who is ONLY obtaining consent should be entered into the table below with the Role "Obtaining Informed Consent".

You have selected that this is either a "transfer", or "transfer with modifications". In the following section, you will be asked to update all personnel associated with your study. This section should indicate all personnel that are currently approved and listed in your IRBNet personnel form. You will need to add each currently approved person to the table below and indicate their role on the study team. If you selected "transfer" and wish to either add or remove personnel to your currently approved study, please go back and select "transfer with modifications". If you have selected "transfer with modifications" you will be able to add new personnel or remove personnel from your approved study in addition to any other changes you may wish to include.

Personnel Supplement

1. Click "save" after each entry.

2. To view linked CITI training information, click "refresh" after personnel entry.

3. If there is no result for the person you are attempting to add, submit a New Contact Form to add this person to the system.

4. If the "CV/Resume on file" field indicates "yes" then a CV has been saved in that person's profile and a CV is not required. If that field is blank, then the individual must add a CV to their profile, or the submitter can attach a CV at the bottom of the card.

Name:
Margaret Haney, PhD
CV/ Resume on file: *No answer provided.*
Role: Co-Investigator
Location: NYSPI
Status at Site (If OMH Site):
☑ Full Time Employee
☐ Part Time Employee
☐ Volunteer
Obtaining Informed Consent: Yes
Assessing Subject Capacity: Yes
CV/Resume:
Margaret Haney CV 2024.pdf

Name:
Felipe Castillo, MD
CV/ Resume on file: *No answer provided.*
Role: Co-Investigator
Location: NYSPI
Status at Site (If OMH Site):
☐ Full Time Employee
☑ Part Time Employee
☐ Volunteer
Obtaining Informed Consent: Yes
Assessing Subject Capacity: Yes
CV/Resume:
Felipe Castillo CV 2024.pdf

Name:
Richard Foltin, PhD
CV/ Resume on file: *No answer provided.*
Role: Co-Investigator
Location: NYSPI
Status at Site (If OMH Site):
☑ Full Time Employee
☐ Part Time Employee
☐ Volunteer
Obtaining Informed Consent: No
Assessing Subject Capacity: No
CV/Resume:
Richard Foltin CV 2024.pdf

Name:
Caroline Alleyne,
CV/ Resume on file: *No answer provided.*
Role: Research Assistant
Location: NYSPI
Status at Site (If OMH Site):
☑ Full Time Employee
☐ Part Time Employee
☐ Volunteer
Obtaining Informed Consent: No
Assessing Subject Capacity: No
CV/Resume:
Caroline Alleyne CV 2023-24-8 (2).pdf

Name:
Alexis Marshall,
CV/ Resume on file: *No answer provided.*
Role: Research Assistant

Name:
Jeanne Manubay, MD
CV/ Resume on file: *No answer provided.*
Role: Co-Investigator

Location: NYSPI
Status at Site (If OMH Site):
☑ Full Time Employee
☐ Part Time Employee
☐ Volunteer
Obtaining Informed Consent: No
Assessing Subject Capacity: No
CV/Resume:
Alexis Marshall_CV 2024.pdf

Location: NYSPI
Status at Site (If OMH Site):
☑ Full Time Employee
☐ Part Time Employee
☐ Volunteer
Obtaining Informed Consent: Yes
Assessing Subject Capacity: Yes
CV/Resume:
Jeanne Manubay CV 2024.pdf

Name:
Caroline Arout, PhD
CV/ Resume on file: Yes
Role: Co-PI
Location: NYSPI
Status at Site (If OMH Site):
☑ Full Time Employee
☐ Part Time Employee
☐ Volunteer
Obtaining Informed Consent: Yes
Assessing Subject Capacity: Yes
CV/Resume:
Arout CV_11.2024.pdf

Name:
Eric Parmon, MD
CV/ Resume on file: Yes
Role: Co-Investigator
Location: NYSPI
Status at Site (If OMH Site):
☑ Full Time Employee
☐ Part Time Employee
☐ Volunteer
Obtaining Informed Consent: Yes
Assessing Subject Capacity: Yes
CV/Resume:
Eric Parmon CV.pdf

Name:
Stephanie Reed, Ph.D.
CV/ Resume on file: *No answer provided.*
Role: Co-Investigator
Location: NYSPI
Status at Site (If OMH Site):
☑ Full Time Employee
☐ Part Time Employee
☐ Volunteer
Obtaining Informed Consent: Yes
Assessing Subject Capacity: No
CV/Resume:
Stephanie Reed-Collins CV

Good Clinical Practice

Contact	Expires (as of 04/14/2025)
Alexis Marshall,	06/20/2123
Caroline Alleyne,	07/10/2123

Contact	Expires (as of 04/14/2025)
Caroline Arout, PhD	01/08/2125
Eric Parmon, MD	06/12/2122
Felipe Castillo, MD	11/15/2124
Jeanne Manubay, MD	07/14/2123
Margaret Haney, PhD	01/09/2125
Richard Foltin, PhD	12/12/2122
Stephanie Reed, Ph.D.	11/09/2124

Basic CITI Training

Contact	Expires (as of 04/14/2025)
Alexis Marshall,	06/20/2026
Caroline Alleyne,	12/15/2026
Caroline Arout, PhD	07/06/2026
Eric Parmon, MD	06/12/2025
Felipe Castillo, MD	01/29/2028
Jeanne Manubay, MD	08/13/2025
Margaret Haney, PhD	01/10/2028
Richard Foltin, PhD	08/26/2027
Stephanie Reed, Ph.D.	11/09/2027

Personnel To Remove

Click "Remove Contact" below, then add the contact to be removed to the list in the pop up window.

No answer provided.

Location Supplement

Will you be conducting activities at more than one site?

No

Please check off all sites where your study will take place under the supervision of Office of Mental Health investigator(s). This includes sites where research teams will physically conduct research, review records, and/or conduct recruitment.

If you have only one location, please select that location. If multiple locations, indicate in any order.
New York State Psychiatric Institute

Facility Director for Main Site

Joshua Gordon, MD

Email: joshua.gordon@nyspi.columbia.edu **Phone:**

Study Details

Describe the purpose of the investigation. If this is a clinical trial, this should include a description of the disease and the goals of the research.

Chronic pain is a significant public health concern in the U.S., for which prescription opioids have historically been the standard treatment. This has resulted in striking rates of opioid use disorders and fatal overdoses. Identifying non-opioid medications for the management of chronic pain with minimal abuse liability is a public health necessity, and cannabinoids are a promising drug class for this purpose. More than 80% of medicinal cannabis users report pain as their primary medical indication. These patients tend to seek products that are low in delta-9-tetrahydrocannabinol (THC; the primary psychoactive, and thus intoxicating, component of cannabis), and high in cannabidiol (CBD), a cannabinoid that purportedly has therapeutic benefit for pain but does not produce intoxicating effects [1]. However, there are few well-controlled human laboratory studies assessing the efficacy of high-CBD cannabis for pain in the context of abuse, and even less is known regarding the effects of daily repeated use of cannabis on pain and its relationship to abuse liability. Carefully controlled research is needed. The proposed randomized, within-subjects, placebo-controlled 16-day crossover inpatient human laboratory pilot study (N = 16 healthy cannabis users; 8 men, 8 women) will address three important gaps in our understanding of the potential therapeutic utility of cannabis for pain: 1) If abruptly switching active cannabis(4.91% CBD/2.98% THC) to inactive cannabis (0% CBD/THC) increases experimental pain sensitivity, i.e. hyperalgesia, relative to baseline and if these effects parallel measures of cannabis withdrawal such as disrupted mood and sleep (Each cigarette contains approximately 39.28mg of CBD and 23.84mg of THC. They smoke 75% of one cigarette, so each dose is approximately 29.46mg of CBD and 17.88mg of THC); 2) If tolerance to the analgesic and abuse- related effects of cannabis is reversed following 7 days of abstinence from active-THC cannabis (by administering 0% CBD/THC, inactive cannabis); 3) If tolerance is present/develops to repeated, daily smoked cannabis (4.91% CBD/2.98% THC) administration on measures of experimental pain and abuse liability. Two distinct modalities of experimental pain will be assessed: The Cold Pressor Test (CPT) and Quantitative Sensory Testing Thermal Temporal Summation (QST-TTS). The study will start with a day of active cannabis administration (4.91% CBD/2.98% THC) given 3x/day in order to standardize cannabis exposure across participants (Day 1), and will be followed by a 7-day "inactive phase" (Day 2-8) in which participants will smoke inactive cannabis (0% CBD/THC) 3x/day during this 7-day period. The last 7 days (Day 9-15) will comprise an "active cannabis phase" in which participants will smoke cannabis (4.91% CBD/2.98% THC) 3x/day. Throughout the study, experimental pain and abuse-related effects will be assessed, as will sleep and subjective mood assessments. With rates of chronic pain increasing and limited availability of safe and effective treatment alternatives to opioids, this study will provide essential data regarding the efficacy of daily cannabis use on measures of analgesia and abuse liability and the consequences of cannabis abstinence on measures of pain, as it is possible that abrupt cessation of cannabis use will lead to worsened baseline pain.

General Overview:
This within-subjects study will examine the effects of daily repeated use of cannabis on pain and its relationship to abuse liability. Healthy, non-treatment seeking cannabis smokers (N=16, 8M, 8F) will be admitted to the research center on 5- South of NYSPI for a 16-day inpatient stay. On the first full inpatient day, participants will smoke active cannabis (4.91% CBD/2.98% THC). Days 2-8 will comprise the Inactive Phase, in which placebo cannabis (0%CBD/THC) will be administered 3x/day. The next 7 days (Day 9-15) will be the Active Phase, in which active cannabis (4.91% CBD/2.98% THC) will be administered at the same time points (Table 1). Participants will complete subjective effects visual analog scales and a cannabis rating form daily, and will complete the Cold-Pressor Test and Quantitative Sensory Testing-Thermal Temporal Summation on Days 1, 2, 5, 8, 9, 12, and 15 to explore three critical questions regarding cannabis' therapeutic utility for pain (as illustrated in Figure 1): 1) If abruptly switching active cannabis to inactive cannabis increases experimental pain sensitivity, i.e. hyperalgesia (Day 2-8; red bars) relative to baseline and if these effects parallel measures of cannabis withdrawal such as disrupted mood and sleep; 2) If pharmacological tolerance to the analgesic and abuse-related effects of cannabis is reversed following 7 days of abstinence from active-THC cannabis (by administering 0% CBD/THC, inactive cannabis): defined as a) significant decrease in CPT latencies and QST-TTS response following active cannabis administration on Day 12 or Day 15 compared to Day 9 (Active Phase), and b) a significant decrease in subjective visual analog scale ratings of abuse, i.e. 'Good Drug Effect' following active cannabis administration on Day 12 or Day 15 (Active Phase) compared to Day 9 (Active Phase); 3)If tolerance is present/develops to repeated, daily smoked cannabis (4.91% CBD/2.98% THC) administration on measures of experimental pain and abuse liability (green bar): defined as a significant increase in CPT latencies and QSTTTS response and 'good drug effect' after active cannabis administration when Day 9 of the Active Phase is compared to Day 1.

Provide the hypothesis for this research.

Aim 1. Determine the effects of abstinence from active cannabis (by use of 0% THC cannabis) on experimental pain. We hypothesize that (a) abrupt abstinence will result in increased CPT and QST-TTS responses, indicative of withdrawal-induced hyperalgesia.

Aim 2. Determine if a) tolerance is present (Day 1) and is reversed following abstinence from active cannabis (Days 2-8); b) tolerance develops to daily smoked active cannabis (4.91% CBD/2.98% THC; Days 9-15) administration on pain and abuse liability measures. We hypothesize that: (a) existing analgesic tolerance will be reversed following abstinence from active cannabis; (b) over the course of the active cannabis phase, tolerance will develop to cannabis' analgesic but not abuse-related effects.

Include pertinent information about the relationship of the proposed research to previous studies and describe the significance of the proposed research. Be brief.

In an attempt to mitigate the ongoing opioid crisis, the CDC and NIH have urged the identification of non-opioid medications for chronic pain. Developing novel pain management approaches with lower abuse liability than opioids is a public health necessity. In light of the widespread legalization of cannabinoids (cannabis or components of the cannabis plant) across the U.S, use of these products is increasing both recreationally and medicinally. Many medicinal cannabis users indicate that they use cannabinoid products to assist with chronic pain management; of the >1.2 million registered medical cannabis patients across the U.S., the majority (>80%) cite pain relief as the primary reason for use. These legislative changes and use patterns are emerging in the absence of sufficient controlled scientific evidence supporting efficacy for pain. Specifically, most people using cannabinoids for pain do so on a daily and long-term basis, yet it is unknown how cannabinoid effects change with repeated use. Of the 100+ cannabinoids identified, the two major and most prominently used are delta9- tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the primary psychoactive component of cannabis and has been shown to exert analgesic effects by our laboratory (Cooper, 2013, p.1984), but its therapeutic utility occurs at concentrations associated with abuse liability. CBD, on the other hand, is non-intoxicating thus is not considered to have abuse liability. For this reason, products that are high in CBD content are being used at increasing rates for various medical conditions ranging from childhood seizures (for which it is FDA- approved as Epidiolex) to chronic pain.

A number of studies have shown combinations of CBD:THC to have analgesic efficacy and minimal abuse liability in populations with chronic pain, including HIV-related neuropathic pain and cancer pain. However, there is very little scientific evidence outside of medically-ill populations to support the therapeutic utility of CBD:THC combinations for pain relief in the context of abuse liability, particularly when used repeatedly. Further, while some studies suggest that CBD attenuates the adverse effects of THC (Osborne, 2017, p.310-324) other studies have demonstrated the opposite (Solowij, 2019, p. 17-35) or no effect at all (Haney, 2016, p. 1974-1982). Despite mixed evidence for efficacy and abuse potential, people using cannabis medicinally often seek out products from dispensaries that are high in CBD and low in THC content due to the widespread belief that these products offer therapeutic benefit without abuse liability (Mead, 2017, p.288-291).

The consequences of daily use of combined smoked CBD:THC cannabis on pain outcomes or abuse-related effects are not known. An additional unknown is how cessation of daily use affects measures of pain. Cannabinoids can increase pain sensitivity at certain doses, but no studies have investigated if pain sensitivity increases as a function of abrupt cannabis abstinence. It is possible that cannabis' analgesic effects diminish with repeated use, resulting in increased use to overcome pharmacological tolerance. Further, abrupt cannabis cessation may result in hyperalgesia along with other symptoms of cannabis withdrawal, which would make maintaining abstinence difficult. These factors could worsen ongoing pain and increase the likelihood of developing cannabis use disorder. Finally, it is unknown if analgesic tolerance can be reversed following a period of abstinence from active cannabis. Currently, there are no data on these effects to inform patients using cannabis on a regular basis for pain.

Study Procedures

Research Procedures (Select all that apply):

- ☐ Data Analysis/ Chart Review
- ☑ Drug Study
- ☐ Device Study
- ☐ MRI w/ Contrast: MRIs for research purposes are subject to CBIN policy on Incidental Findings
- ☐ MRI w/out Contrast: MRIs for research purposes are subject to CBIN policy on Incidental Findings
- ☑ Interview/Survey/Questionnaire
- ☑ Blood Collection
- ☑ Sample Collection other than blood
- ☑ Non Invasive Physical Measurements
- ☐ Student Research
- ☐ Ionizing Radiation
- ☐ IV Infusion
- ☐ Genetic Research
- ☐ Transcranial Magnetic Stimulation (TMS)
- ☐ Transcranial Direct-Current Stimulation (tDCS)
- ☐ Requesting that NKI serve as the IRB for an institution outside of OMH/RFMH
- ☐ Establishment of a Research Repository

Sample Collection Other Than Blood

- ☑ Urine
- ☐ Cerebral Spinal Fluid (CSF)
- ☑ Other

Specify Other
COVID-19 nasopharyngeal swabs

Detail all questionnaires and assessments (including validated assessments) that will be used for this study.

These items can be explained or listed and attached. If the assessment or questionnaire is validated, please confirm that there have been no modifications to the document. If the study instrument is not a validated tool please attach the document with this submission.

Some assessments are conducted under a screening protocol (#7091R), while others are conducted under the study protocol (#8016), which is indicated below.

Screening Assessments (these assessments (which are validated and not modified from their original form) are conducted under screening protocol 7091R and are thus not part of protocol 8016, but are detailed for clarity in our procedures):

1) Telephone Interview: 15 min.
2) Timeline Follow-Back Interview for substance use: 10 min.
3) Drug Use History Questionnaire: 10 min.
4) General Health Questionnaire: 5 min.
5) Medical History Questionnaire: 10 min.
6) Beck Depression Inventory: 5 min.
7) General Pain Index Questionnaire: 5 min.
8) Structured Clinical Interview for DSM-5: 30 min.
9) 12-lead electrocardiogram: 15 min.
10) Laboratory Tests (blood count with differential chemistry profile, liver enzymes, and GGTP): 30 min.
11) Urinalysis with 12-panel urine drug testing: 5 min.
12) Physical and Psychiatric Examination: 30 min, unless there is an indication for a diagnosis, in which case it will be 90 min.

Experimental Assessments (conducted under protocol 8016):

1) The Cold Pressor Test (CPT) is a validated and reliable pain-induction procedure that reflects A-delta nerve fiber
activity within the autonomic nervous system and closely mimics clinical chronic pain. CPT has been shown to have
excellent reliability and predictive validity for medication-induced analgesia, including cannabinoids. For this task, two
temperature- controlled circulating water baths maintain warm (36.5-37.5ºC) and cold (3.5-4.5ºC) water. Participants
immerse their hand into a warm bath for 3 min (to standardize baseline skin temperature), then the cold bath, indicating when they first experience pain and withdrawing when the pain gets uncomfortable. Study staff will record time (in seconds) until participants: 1) report discomfort (pain threshold), and 2) withdraw their hand from the cold water (pain tolerance): 15 min.

2) Quantitative Sensory Testing-Thermal Temporal Summation (QST-TTS) uses repetitive fixed frequency and intensity
heat stimulation to induce central sensitization of C-fibers in the spinal cord and is regarded as an experimental
correlate of the 'wind-up' phenomenon in the dorsal horn. As dorsal horn CB-1 activity has been linked to suppression of 'wind-up' and central sensitization (the mechanism purportedly underlying cannabis' efficacy for neuropathic pain),
cannabis use may decrease QST-TTS response, mirroring analgesia on the CPT during active cannabis administration vs. placebo. For this task, a Medoc TSA-II NeuroSensory Analyzer with a 30 x 30 mm Peltier thermode applies tonic noxious heat stimulation to the thenar eminence of the palm: the baseline temperature is 32.0°C, increases at a rate of 1°C/s up to 46.5°C, and remains constant for 120 sec. Total duration: 3 min.

3) Cold Pressor Test Visual Analog Scale (CPT-VAS): 11-item questionnaire rating the physiological and subjective effects of the cold water on a 100 mm VAS after the CPT: 15 sec.

4) Quantitative Sensory Testing-Thermal Temporal Summation Computerized Visual Analog Scale (CoVAS): Participants
rate magnitude of perceived pain on a 100 mm VAS during the QST-TTS: 135 sec.

5) Physiological response to pain: Heart rate and blood pressure will be measured throughout pain assessments: 2 min.

6) Pain Intensity/Bothersomeness Scale (PIBS): Ratings of CPT and QST pain on a 0-to-10 scale: 0 being 'not
painful/bothersome at all' and 10 being 'most painful/bothersome feeling imaginable': 10 sec.

7) Subjective Effects: A series of 100 mm VAS in which participants indicate how they are feeling at that

moment will be completed 3x/day. The 44-item VAS includes mood, physical symptom, and drug effect descriptors. Based on a cluster analysis, we employed arithmetic means of individual item scores to reduce 34 of the 44 items into eight subscales: good drug effect; miserable; irritable; anxious; bad effect; social; and confused. We also analyze individual VAS drug craving ratings. These subjective measures may detect changes in abuse-related effects as well as changes in mood (miserable, irritable, anxious, cannabis craving) as a function of cannabis condition: 3 min.

8) Objective Sleep Measures: Participants will wear an Actiwatch Activity Monitoring System that tracks gross motor
activity (Actiwatch®: Respironics Company, Bend, OR) and records objective sleep outcomes (hours slept, number of
awakenings). We have used this system effectively to demonstrate perturbations in sleep as a function of cannabis
withdrawal.

9) Sleep Questionnaire: Participants will complete a sleep questionnaire which consists of a 7-item, 100 mm VAS
instrument that assesses the quality of sleep and how many hours slept the previous night and wakefulness in the
morning. Participants will be asked to rate symptoms by placing a mark on a line representing a continuum from "not at all" (on the left of the line) to "extremely" (on the right of the line) indicating how the phrase relates to the last night's sleep: 30 sec.

10) Cannabis Rating Form (CRF): Participants rate the strength, liking, desire to take again, good drug effect and bad
drug effect of cannabis on a 100mm VAS: 2 min.

Please attach all Questionnaires and Assessments listed above.
No answer provided.

Describe the procedures in sufficient detail so that a reviewer, who is not familiar with them, can comprehend what is to be done and can evaluate any risks.

This study is now in data analysis only, and the following procedures describe the study as it was approved and conducted during the COVID era.

Consent Procedures:

Step 1 (conducted under #7091R). After initial determinations of eligibility (e.g. current drug use patterns, attitude about treatment) obtained via the telephone interview, volunteers will be emailed a secure link to a Qualtrics survey containing assessments regarding demographic and medical information, thereby eliminating the need for subjects to travel to NYSPI to complete these questionnaires and thus reducing their risk of exposure to COVID-19 by traveling to the institution or while on site. They will be asked to review our screening and evaluation consent form (IRB #7091R), as well as the study consent form, HIPAA form and NYSPI privacy practices. Copies of the study consent form and the HIPAA form will be sent to participants via encrypted email. Participants will be required to select YES/NO to indicate whether they reviewed these documents and agree to complete the assessments before they may continue.

Step 2 (conducted under #7091R). Interviews with a trained psychologist will occur via HIPAA-compliant virtual telemedicine platforms such as Apple Facetime or Webex, once again minimizing the risk of exposure to COVID-19 that would exist if requiring all subjects to travel to NYSPI for an in-person interview. Psychologists (Drs. Arout, Haney, Kearney-Ramos, Harris) will conduct interviews regarding drug use and psychiatric symptoms and will provide a detailed explanation of the procedures outlined in the consent form. If the volunteers are eligible for continued screening after the PhD interview, they will be invited fora single in-person screening visit to review the study consent form, complete medical assessments, and be tested for COVID-19. A dated note-to-file will be included in the participant's chart of the remote/verbal consent procedure documenting the consent discussion and review of the consent form, along with the participant's electronic agreement of the consent, as signed by the consenter.

Step 3 (conducted under #8016). During the single in-person screening visit, participants will review and sign the study consent form after reviewing it with a study physician. Medical and psychiatric interviews will be conducted by a physician in the Division on Substance Abuse (e.g. Drs. Castillo, Manubay, Parmon), and will include a physical examination, nasal COVID-19 test, and review of medical results and study inclusion/exclusion criteria. All of our psychiatrists have completed at least 4 years of psychiatric training and most are Board Certified (those not Board Certified are in the process of obtaining certification). Physicians will determine whether volunteers have current Axis I psychopathology (e.g. major depressive episode, bipolar disorder, schizophrenia) requiring medical intervention. The physicians discuss this protocol with the volunteers and document their consent to the research study. No study procedures will begin until the physician verifies the participant meets inclusion/exclusion criteria, understands the medical risks of participation, and is capable of providing informed consent. Dr. Manubay, the senior study physician, will settle any disagreements among the study team as to a volunteer's eligibility, and will make the final decision as to study participation. All procedures are consistent with the Division of Substance Abuse Guidelines for Investigators (9/8/08). Research staff will perform laboratory tests (ECG, blood draw, urinalysis) for medical screening with study physicians. Psychologists will sign the study consent form after volunteers complete medical and further psychiatric evaluation with study physicians. Thus, several interviews in which drug use is proved will be conducted with volunteers prior to telling them the nature of the study. In this way, we minimize the probability that they will misrepresent their drug use in order to gain entry into the research. Volunteers expressing interest in treatment at any point during participation will be given an immediate treatment referral.

Step 4 (conducted under #8016). Following the physical and consent, volunteers will re-read the study consent form and procedures with study personnel, practice study tasks, and complete a multiple choice consent quiz that covers pertinent study procedures. This multi-consent process provides participants with new information at each decision point. Volunteers will have spent time in the laboratory engaging in the behaviors and tasks required for full study completion. These procedures provide fully informed consent and will allow study personnel to accurately determine a volunteer's capacity to provide fully informed consent.

Study participants are informed of the risk of exposure to COVID-19 while traveling to our facility and while completing research activities on site, as well as all safety guidelines enacted by NYSPI, during the initial phone interview with research staff, the PhD interview, and during the consent discussion conducted with a physician during their physical examination. Thus, this new risk and ways to minimize this risk are communicated to study participants at each step in the screening process. Participants will always be given the option to reschedule their visit to our facility if they do not feel comfortable traveling to their appointment (for example the subway is too crowded). This will be noted as part of the consent procedures.

Laboratory Facility. All cannabis administration time-points and tasks will be conducted in the Substance Use Research Center (SURC) located on the 3rd floor of the NYS Psychiatric Institute. The time-points and tasks described in this protocol will be conducted in the Outpatient Cannabis Laboratory. The laboratory has two testing rooms that are adjacent to a control room. The testing rooms are equipped with a workstation consisting of a worktable, a comfortable chair, and a Macintosh computer

networked with computers located in the adjacent control room used to collect subjective-effects data. The test rooms are also equipped with automatic sphygmomanometers, electrocardiography systems, CPT apparatus, a mini refrigerator, and microwave. The control room oversees the test rooms via a one-way mirror. It contains office and storage space and Macintosh computer systems with a Hewlett Packard Laser Jet printer. Macintosh computers in the control room are used to run sessions and to automate data collection. Participants are continuously monitored through one-way glass and are able to communicate with the investigators via an intercom. The control room also houses ancillary computer equipment and physiological monitoring equipment (heart rate, blood pressure monitor, pulse oximeter unit). Participants will sit in a comfortable task chair in front of a Macintosh computer. A response manipulandum ("mouse") will be used for completion of pain rating scales and subjective-effects questionnaires.

Screening Process: (also see details under Consent Procedures regarding remote procedures). Eligibility screening for this study will be conducted under IRB protocol 7091R. As described in the 7091R protocol, the screening process will consist of:

1) several self-report questionnaires and 2) several structured clinical interviews conducted remotely and on the in person screening visit, participants will have 3) vital signs, height and weight, 4) urine and blood samples for routine laboratory tests and drug screening, a nasal swab test for COVID-19, 5) an ECG, and (6) a physical examination. Drug interviews, psychological and general assessments related to study issues will be conducted by PhDs who have had extensive experience in these procedures. All of these procedures will be done under protocol #7091R. Participants deemed eligible for further screening after the PhD interview will be invited to come to the laboratory for an in-person visit, during which they will sign the Screening Consent Form under IRB protocol 7091R (before proceeding with additional screening procedures).

Training Session: All potential participants who meet inclusion/exclusion criteria will undergo a training session on the CPT and QST-TTS prior to admission into the study, since there is a proportion of the population that is unable or unwilling to tolerate pain induced by the CPT and/or the QST-TTS.

Cold Pressor Test: The CPT apparatus consists of two refrigerated circulators, filled with warm (36.5-37.5°C) and cold (3.5- 4.5°C) water. At the beginning of the procedure, a research assistant (same gender as the participant) will read a script describing the procedure to the participant, as well as take their blood pressure and heart rate as a safety assessment and for baseline values. Participants will then insert their non- dominant hand into the warm water and remove it after 3 minutes; skin temperature of the thumb pad will be measured. Blood pressure and heart rate will be taken halfway through the 3-minute period in the warm water tank. Participants will then insert their hand in the cold water and will be instructed to report when they first experience pain (pain threshold) and remove their hand when the cold water can no longer be tolerated (pain tolerance). Maximum immersion time will be 3 minutes. Immediately after hand removal, blood pressure, heart rate, and skin temperature will be measured. Participants will then complete measures of CPT-induced discomfort (described below). Individuals who do not report pain and/or do not remove their hand within 3 minutes will be excluded. If at any point that vitals are taken systolic pressure is greater than or equal to 180, diastolic pressure is greater than or equal to 110 (each measure monitored and confirmed by a manual reading), in which either is sustained after a manual redo for more than 120 seconds, will result in suspending the CPT for that participant for that given day. If a single reading of systolic blood pressure is greater than 200, or a single reading of diastolic blood pressure is greater than 120 (each measure confirmed by a manual reading), or a confirmed heart rate greater than 160, the CPT session will be immediately suspended for the participant that given day. Additionally, for either parameter, the participant's vital signs will be assessed every thirty minutes until it stabilizes within normal range under the guidance of the study physician. In the event that vital signs are not stabilized, we will assess the participant as described in the Criteria for Early Discontinuation section.

Quantitative Sensory Testing-Thermal Temporal Summation. The QST-TTS apparatus is a thermal testing analyzer with a 30 x 30 mm Peltier thermode, which will use repetitive nociceptive heat stimulation of a fixed frequency and intensity. At the beginning of the procedure, a research assistant (same gender as the participant) will read a script describing the procedure to the participant. Tonic noxious heat stimulation will be applied to the palm using a ramp-and-hold method, in which the baseline temperature will be set at 32.0°C, and will increase at a rate of 1°C/s up to 46.5°C, remaining constant for 120 sec. During the total duration of stimulation (135 seconds), participants will continuously rate the magnitude of perceived pain (described below). Individuals experiencing neurosensory deficits will be excluded.

Inpatient Phase (Table 2; attached)

Day -1 Check-In Procedures. Eligible participants will be admitted into the 5-South inpatient unit. Although we will have open enrollment, we aim to maximize enrollment of up to three participants on the move-in day, or as many as the 5th floor can accommodate at that time. Move-in procedures will include a non-invasive strip search, a urine drug screen test, a urine pregnancy test for women, vital signs (sitting blood pressure and heart rate), weight, breathalyzer test for ethyl alcohol (EtOH), a timeline follow back interview, and verification of eligibility. Participants will be trained on computer tasks and cannabis smoking procedures before data collection begins.

Days 1-15 Study Procedures

Participants will be awakened at approximately 0700h on study days and lights out each night at 2300h by 5-South staff. At 0800h, participants will receive breakfast. At 0900h, participants will be bought down to the third-floor outpatient room to have vital signs taken (seated blood pressure and pulse rate) and to complete a sleep questionnaire, precannabis administration. Actiwatches will be put on both wrists each night and will be collected each morning.

Day 1 (Standardization)

Since we will recruit moderate-heavy cannabis users with varied use patterns, they will enter the study with varying pharmacological tolerance. Therefore, Study Day 1 will be an initial day of active cannabis administration to standardize exposure to the same strength of smoked cannabis across participants prior to enforced abstinence from active cannabis in the Inactive Phase (Day 2-8). Participants will be administered active cannabis (two one 4.91% CBD/2.98% THC cigarettes) at 1000h, 1300h, and 1600h.

Days 2-8 (Inactive Phase)

On Study Days 2-8, participants will be administered one inactive cannabis cigarette (0.00% CBD/THC) at the same three time-points (1000, 1300, 1600). We have shown that inactive cannabis controls for expectancy effects of smoking, producing small but reliable increases in ratings of 'high' [5]. Therefore, this phase will assess how abstinence from active- THC cannabis affects pain outcomes in parallel to measures of cannabis intoxication and withdrawal (mood, sleep).

Days 9-15 (Active Phase)

On Study Days 9-15 participants will be administered an active cannabis cigarette (one 4.91% CBD/2.98% THC cigarette) at the same three time-points (1000, 1300, 1600), with the exception of Day 15 where they will be administered active cannabis only at 1000. This phase will allow us to see if CPT and QST pain outcomes and abuse liability change over time

Move Out

Following completion of all assessments of Day 15, the PI will discuss with the participants benefits of cannabis
cessation, highlighting availability of a range of treatment options, prior to discharge. At 180 minutes post-cannabis administration, participants will complete field sobriety tests, vital signs, and a Mini-Mental State Exam (MMSE), and will be permitted to leave once they meet discharge criteria. Criteria for discharge will be met when participants report no ongoing subjective drug effects and have no signs of impairment or intoxication, pass the field sobriety test, have normal vitals, and a normal mental status score as assessed by the MMSE. Dr. Arout, Haney, or Kearney-Ramos will make the final determination that the patient is sober and medically stable and can leave the facility.

The effects of smoked cannabis are typically gone within 3 hours. In the rare event that a participant is still impaired at the conclusion of Study Day 15, they will be asked to remain in the laboratory until the effects wear off, and will be paid extra (i.e., $10 per hour for any additional time they remain in the laboratory). Participants may be sent home in a taxi, for which they will be reimbursed. They will be allowed to leave the facility when they pass the field sobriety test and are medically stable. They will be instructed not to drive a car or use other drugs or alcohol for 8 hours after administration of cannabis; therefore, participants will be required to take public transportation (i.e., bus or subway) from the laboratory on Day 15, for which they will be reimbursed (included in their pay for Day 15).

CPT and QST-TTS

On Days 1, 2, 5, 8, 9, 12, and 15, participants will complete the CPT and QST-TTS pain tasks 30 minutes before the 1000h cannabis administration (baseline), and 0, 15, 30, 45, 60, and 90 minutes post-cannabis administration. Participants will also complete measures of CPT-induced discomfort (CPT-VAS, PIBS) and will continuously rate the magnitude of perceived pain for the temporal heat stimulation of the QST-TTS (Co-VAS) at these time-points. On these days of pain testing, except for Day 15, participants will also complete a cannabis rating form and subjective effects visual analog scales pre-cannabis administration (0945h), for a full-time course after the first cannabis administration (1015h, 1045h, 1115h, 1145h, 1215h), and after each subsequent cannabis administration timepoint (1315h, 1615h). On Day 15, these assessments will conclude with the 1215 time-point. Vital signs will be taken before and after each pain assessment. In addition, vital signs will be taken halfway through the duration of each CPT assessment. If vital sign parameters are exceeded at any point during the CPT task, staff will follow the same assessment procedures as stated in the training section above.

On days when there are no pain assessments, participants will complete just the cannabis rating form and subjective effects battery at 1015h, 1315h, and 1615h.

Cannabis Administration

Cannabis (active: 4.91% CBD/2.98% THC and inactive: 0% CBD/THC) will be provided by the National Institute on Drug Abuse (NIDA). At three timepoints each day, participants will smoke 75% of one cannabis cigarette (800 mg) at each time point (1000, 1300, 1600) using our standardized paced puffing procedure [6]. Using an intercom, an investigator will signal 'light the cigarette' (30 sec), 'prepare' (5 sec), 'inhale' (5 sec), 'hold smoke in lungs' (10 sec) and 'exhale' with a 40-sec interval between each puff; cannabis administration will be blind to the participant.

Explain the reason(s) subjects may be withdrawn or terminated from the study.

If you do not anticipate withdrawing or terminating subjects from the study, please state that in this box.

Withdrawal Criteria and Procedures.

--Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw subjects from the study for any of the following reasons: non-adherence to protocol requirements; unwillingness to continue in the study; medical judgment of the Investigator.

Withdrawal of Subjects from Study.

--Subjects must be withdrawn from study therapy and withdrawn from the study if any of the following occur: In the Investigator's medical judgment, further participation would be injurious to the subject's health or well-being (as determined by the study physician); Positive serum or urine pregnancy test, confirmed by a serum pregnancy (serum human chorionic gonadotropin) test result; AEs occurring that in the opinion of the Investigator may constitute a potential risk for continued participation by the subject (e.g., extreme paranoia resulting from cannabis administration); Major protocol violation as discussed and agreed upon between the Sponsor and Investigator; Consent is withdrawn; Termination of the study by the Sponsor; Termination of the study by the local health or regulatory authority or Institutional Review Board (IRB).

COVID-19 Early Discontinuation Procedures.

--Participants will be removed from the study if they display any symptoms of an upper respiratory infection (cough, fever, coryza). The appropriate referral will be made (e.g. emergency department, home with outpatient follow up via telemedicine) depending on the participants clinical status. COVID-19 testing may be performed prior to discharge; if so results conveyed to the participant when results return in 3-4 days. If sent home, participants will be instructed to self-quarantine until the COVID-19 tests results are available, and further recommendations made upon test results

Participant Study Termination Resulting from Adverse Events from Pain Testing.

--The Cold Pressor Test (CPT) may induce a rise in blood pressure and/or heart rate. If this occurs (to standards described below), the CPT will immediately be stopped, and the participant will be withdrawn from the study if heart rate or blood pressure values exceed safe limits. Emergency medical equipment is available in our laboratory, which is in a hospital where a full medical emergency back- up team is constantly available. Participants will perform the cold pressor test during training, and if their heart rate exceeds 160, their systolic blood pressure exceeds 180, or their diastolic blood pressure exceeds 110, they will be discharged from the study by the Investigator. Vital signs will be taken before, during, and after the CPT assessment during training. During laboratory sessions, if systolic blood pressure of greater than 180 or a diastolic blood pressure greater than 110 (each measure confirmed by manual reading), in which either is sustained for more than 120 sec. is observed, the CPT for that participant will be suspended for that given day. In addition, a single reading of systolic blood pressure greater than 200, or a single reading of diastolic pressure greater than 120 (each measure confirmed by manual reading), or a confirmed heart rate of greater than 160, will result in suspending the CPT for that participant for that given day. If any of these parameters is exceeded, we will immediately confer with a staff internist to determine whether the episode of hypertension or tachycardia is resolving and can be followed up on an outpatient basis, or whether acute medical intervention is indicated. We will also continue to take that participant's vital signs every 30 minutes until the episode has resolved or until a staff internist determines that acute medical intervention is indicated. If these changes are observed on a second occasion, the CPT will not be administered again to that participant.

Drug Supplement (1 of 1)

Please fill out this Drug Supplement for EACH drug. Once completed click "Repeat" at the bottom of the page to enter another drug. Once all drugs have been entered click "Next"

Please enter the name of the study drug.

Cannabis

Is the drug approved by the FDA?

No

Is the drug being used in accordance with labeling?

No

Does use of the drug meet the requirements for exemption from IND requirements?
No

Has an IND been issued by the FDA?

For more information on Sponsor-Investigator responsibilities, please refer to: ***FDA Information***

Yes

Provide the IND number.
36369

Name the person/entity that holds/is the Sponsor of the IND.

If the IND holder is an OMH investigator, please contact the IRB for information on responsibilities of Sponsor-Investigators.

Meg Haney, Ph.D.

Please attach any correspondence from the FDA with your submission.

IND Ownership Transfer to Dr. Haney 2023	FDA Correspondence
RWF IND 036369 updates_8016_9.26.22.pdf	FDA Correspondence
rwf IND Form of Notice_8016.pdf	FDA Correspondence
RWF IND_1571+PSF_add 8016_6.8.22.pdf	FDA Correspondence

Subjects

Target Enrollment:

This refers to the target subjects enrollment, i.e., the number of subjects necessary to complete research objectives.

20

Total number of subjects requested to reach target enrollment:

This refers to the estimated number of subjects you must "over-enroll" to meet your target enrollment either by active screening or review of records for eligibility.

24

Please identify the groups of the study and how many subjects will be enrolled in each group.

*Click **"save"** at the end of each row.*

***If you have multiple groups**, please use the number (#) assigned to each group on the left of this table to indicate that group in the inclusion/exclusion criteria table (to specify which inclusion/exclusion criteria belong to which subject group).*

Numbers here should equate to the number entered for Target Enrollment.

#	Subject Group	Subject Number
1	Healthy, non-treatment seeking heavy cannabis smokers	20

Please provide a justification for your sample size.

Power calculations were performed using G*Power, with the following assumptions: significance level of α = 0.05, effect size (Cohen's d) of 0.7, and within-subjects correlations of 0.6 for repeated measures. Based on our residential laboratory studies in cannabis smokers, we estimate that 4 of the 24 participants may drop out. The large within-subject correlations (typically ranging from 0.60-0.95) between conditions (active cannabis vs. inactive cannabis) allow for sufficient statistical power with n=20 completers.

Inclusion & Exclusion:

Give detailed inclusion and exclusion criteria (per group, if you have multiple groups). Note that order does not indicate importance. Click Save at the end of each row to both save data and to add a new row. For the final row, click Save and leave the new row blank.

Remember, if you have multiple groups, the column labeled as "Subject Group #" should match the number (#) in the column "#" from the Subject Group table (section above).

Inclusion Criteria

Subject Group #	Inclusion Critereon	Method for Ascertainment
1	Males or females, 21-60 years old	Medical exam, patient-provided identification
1	For women: not pregnant or breastfeeding, and using an acceptable form of birth control (e.g., condoms, IUD)	Self-report during clinical interview and medical exam, urine pregnancy test conducted under screening procedures and on move-in day
1	Reports smoking cannabis ≥ 5 days per week, equivalent to ≥ 2 joints (~0.4 grams/joint) per day for > 4 weeks prior to screening	Self-report during clinical interview and medical exam, urine toxicology
1	Not seeking treatment for cannabis use	Self-report during clinical interview and medical exam
1	Able to provide informed consent	Self-report during clinical interview and medical exam
1	Able to perform study procedures	Self-report during clinical interview and medical exam, training sessions
1	Participation in Screening Study #7091R	Enrollment and completion of screening study #7091R

Exclusion Criteria

Subject Group #	Exclusion Criterion:	Method for Ascertainment
1	Meets DSM-V criteria for any Substance Use Disorder other than cannabis, nicotine or caffeine	Self-report during clinical interview and medical exam
1	Uses other illicit drugs ≥1 day/week in the prior 4 weeks	Self-report during clinical interview and medical exam, urine toxicology
1	If medical history, physical and psychiatric examination, or laboratory tests performed during the screening process revealed any significant illness that the study physician deems contraindicated for study participation (e.g., hypertension, defined as BP >140/90 and/or resting heart rate (HR) > 90)	Self-report and current medication use during clinical interview and medical exam, bloodwork
1	Current illicit use of medical cannabis, Rx analgesics, daily OTC or supplement use, or	Self-report during clinical interview and medical

Subject Group #	Exclusion Criterion:	Method for Ascertainment
	any medications that may affect study outcomes	exam
1	Current pain	Self-report during clinical interview and medical exam
1	Insensitivity to the thermal stimuli of the Cold Pressor Test or Quantitative Sensory Testing	Training session
1	Nicotine users, defined as smoking > 10 tobacco cigarettes/Day in prior 4 weeks, as nicotine use and withdrawal has demonstrated significant effects on pain perception	Self-report during clinical interview

Demographics:

Demographics collected

Please complete the below fields to report your anticipated recruitment demographics.

If you are targeting a specific gender, age, race, or ethnicity, please indicate in the Inclusion Criteria.

Population Gender	Population Age	Population Ethnicity	Population Race
☑ Male	☑ 18-65	☑ Hispanic or Latino	☑ American Indian or Alaska Native
☑ Female	☐ >65	☑ Not Hispanic or Latino	☑ Asian
☐ Transgender/non-binary/non-conforming	☐ 0-7		☑ Black or African American
	☐ 8-17		☑ White
			☑ Native Hawaiian/other Pacific Islander

Indicate all vulnerable populations that will be enrolled in this research (select all that apply).

Only indicate subjects who will be targeted for enrollment.

Pregnant women=Women who are pregnant upon enrollment. Although not targeted, if your protocol will follow women who become incidentally pregnant during the course of the study, please check this box.

NONE=No Vulnerable Populations will be enrolled in this research.

☐ Children
☐ Prisoners
☐ Pregnant Women
☐ Fetuses/Neonates
☐ Individuals with impaired decision making
☐ Illiterate subjects
☐ Non-English speaking subjects
☑ None of the above regulatory considered categories.

Indicate all other research populations of interest that will be enrolled in this research (select all that apply).

- ☐ Inpatient
- ☐ Adults over the age of 60
- ☐ A mental hygiene 33.13 archival
- ☐ Research on students
- ☑ None of the above considered categories

Recruitment

Describe the recruitment process, including how subjects will be identified and selected for the study. Describe in detail how participants will be recruited including methods such as advertisements, private practices, clinics, phone screening, review of records, use of websites, etc. Be sure to include the following information in your description:

- **When, where, by whom and how potential participants will be approached.**
- **If posting on your Facebook page or other social media sites, please explain.**
- **If you will recruit by e-mail, phone, etc., explain how the researcher will obtain the participants' contact information.**

Please be reminded that researchers cannot directly approach a patient for recruitment until that patient has been informed of the study by their physician or a member of their treatment team who has ascertained that the patient is willing to discuss the study with the investigators.

Recruitment is the first step of the informed consent process and should be considered in terms of the first interaction with the subjects or their data.

Is direct contact with subjects being used for this study?

Yes

Are you using a pre-screening process for subject selection?

Pre-screening is used for selecting and finding research participants prior to consent.

Yes

Please describe the pre-screening process.
Potential participants will complete a telephone interview to assess initial eligibility (conducted under screening protocol (7091R) before being invited for in person screening. After reading, discussing, and signing informed consent, volunteers will complete two screening visits. The first will be conducted under screening protocol 7091R, which includes a physical examination by the study physician, as well as lab work (routine bloodwork and urine toxicology). The second will be conducted under 8016, after initial eligibility is confirmed under 7091R. Two separate consent forms and HIPAA forms will be signed (one for 7091R, and one for 8016).

Describe the recruitment process

Eligible participants will be recruited from the New York, NY area. Recruitment for this study will occur primarily through advertisements in local newspapers, online through Craigslist and Columbia's RecruitMe, and by word of mouth. Potential participants will be screened for initial eligibility for cannabis lab studies under our IRB-approved screening protocol (7091R). If they meet general eligibility criteria, they will be screened for study-specific criteria under 8016. Therefore all 8016 participants will be selected from 7091R participants.

At any point in the study, will you (select all that apply):

*For more information on PII/PHI visit **NKI PHI & PII Policy***

- ☐ Request doctor referrals for selection of potential subjects
- ☐ Request information (i.e. subject Personally Identifiable Information (PII) and/or Private Health Information (PHI)) from a record information system
- ☑ Access information (i.e. subject Personally Identifiable Information (PII) and/or Private Health Information (PHI)) from a record information system
- ☑ Use advertisement materials (i.e. flyers, phone calls, emails, etc.)
- ☐ None

Indicate how you will obtain data from the record system (select all that apply):

- ☑ Obtaining record system hard copy records specific to research subjects
- ☑ Obtaining data from a record system digitally

If you are obtaining data from a health record information system(s), you will need to indicate whether you plan to receive a data extract or whether you plan to access the information system(s) directly to create a data set.

Extract *is when the facility responsible for housing/safeguarding the record system provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided with identifiers, or as a de-identified dataset with no way of linking any identifying information.*

Access *to an information system means that the researcher may directly access a health record information system and create a data set for the research study.*

Please list each system from where data will be obtained. Then indicate if you plan to *Access* or *Extract* the data from the system.

*In order to add additional systems click "**save**" at the end of the entry.*

Information System	Obtaining Data	
KisEMR	☑ Access	☐ Extract
SURC server	☑ Access	☐ Extract

Do you intend to receive only de-identified data from the record system(s) in your research study?

No

Indicate which recruitment methods will be utilized. Select all that apply:

- ☑ Flyers
- ☑ Newspaper Advertisement
- ☐ Radio/Television Advertisement
- ☑ Online Advertisement--Including Social Media
- ☐ Letters or Emails
- ☐ Phone Call
- ☐ Group or Class Presentation
- ☐ Other

It was indicated that flyers will be used as recruitment in this study. Please attach flyer(s) below.

It was indicated that Newspaper Advertisements will be used as recruitment in this study. Please attach Newspaper Ad(s) below.

It was indicated that Online/Social Media Advertisements will be used as recruitment in this study. Please attach text, page mockup, or description of posting including any images below.

Please attach all recruitment materials

Must be a Word Doc

8016 advertisement Advertisement

Consent & HIPAA

Select all applicable methods of consent below to indicate the informed consent process that will be used.

☑ Signed Consent

☐ Waiver of signed Consent

Check here indicating that a waiver of consent documentation is being requested in accordance with Federal Regulations 45 CFR 46.117 / 21 CFR 56.109.

Common procedures where this applies includes, but are not limited to:

- *Use of telephone consent or phone screening (provide a copy of the screening script if this choice is made)*
- *Use of internet surveying (provide the method that the survey will be distributed and language that will be provided to the subjects)*
- *A signed consent would jeopardize the subject (provide the consent document that will be handed to the subject. This document should not contain signature lines)*

☐ Alteration to Consent

Check here indicating that an alteration to the elements of consent is being requested in accordance with Federal Regulations 45 CFR 46.116 / 21 CFR 56.109

Common reasons to indicate this choice include

- *Use of deception in research. Explain in study procedures why deception is warranted and detail the elements of consent that will be excluded. Please also provide your plan for debriefing (who will conduct debriefing and when). Please sure to include your debriefing form.*

☑ Full Waiver of Consent

Check here indicating that a waiver of consent is being requested in accordance with Federal Regulations 45 CFR 46.116 / 21 CFR 56.109.

Common reasons to indicate this choice include

- *Chart reviews, archival data (i.e. MHL 33.13), etc.*

Per earlier selections, Illiterate and/or Non-English speaking individuals are being excluded. New York State requires the inclusion of these groups in studies obtaining written or verbal consent, unless justification is provided. Please provide a justification for the exclusion of Illiterate and/or Non-English speaking individuals.

Illiterate and/or Non-English speaking individuals are excluded from this study because they would not be able to accurately respond to the written data collection instruments, which would negatively impact data integrity.

A protocol which does not include an informed consent process may be approved by the IRB under certain conditions. To request IRB approval of a protocol which does not include an informed consent process, please provide a response to all of the following questions. Please be specific in explaining why each statement is true for this research. Completion of this box implies the research (or portion of the research for which the waiver was requested) involves no more than minimal risk to the subjects.

**Use of identifiable information/biospecimens to identify potential subjects (i.e., screening for recruitment purposes) is allowed without informed consent under certain circumstances. A waiver of consent will no longer be needed for these screening activities.*

Explain why and how the research involves no more than minimal risk to the subjects.
While the overall study does involve more than minimal risk (drug administration), we are asking for a waiver of signed consent for screening purposes which do not present more than minimal risk. Participants give electronic and verbal consent during the 7091R screening process, during which PHI is obtained. When they come to NYSPI to complete additional screening, they sign a hard copy of the consent form.

Explain why the waiver will not adversely affect the rights and welfare of the subjects.
Participants sign a hard copy of the consent form when they come to NYSPI to complete additional screening procedures.

Is the research team collecting identifiable private information and/or identifiable biospecimens?
Yes

If yes, explain why the research could not practicably be carried out without using such information or biospecimens in an identifiable format.
They complete preliminary screening, which includes collection of PHI (name, age) over the phone.

Explain why the research could not be practicably be carried out without the waiver of informed consent.
They complete preliminary screening over the phone following verbal consent, which includes collection of PHI (name, age).

If a waiver of informed consent is approved by the IRB, will subjects be provided with additional pertinent information after participation?
No

Explain/describe why or why not
Participants receive all necessary information verbally over the phone. When they come to NYSPI, they sign a hard copy of the consent.

Will any of the study procedures include collecting photographs, audio recordings, and/or video recordings?

For guidance see our policies on your dashboard in the Notices section

This would include collection of MRI images.

N/A – No photos, audio or video recordings will be taken

Identifiable Information

Does this study use or collect any of the below?

- ☑ Names
- ☑ Medical record numbers
- ☑ Phone numbers
- ☐ Fax numbers
- ☑ Electronic mail addresses
- ☑ Social Security numbers
- ☐ Account numbers
- ☐ Certificate/license numbers
- ☐ Device identifiers and serial numbers
- ☐ Web Universal Resource Locators (URLs)
- ☐ Internet Protocol (IP) address numbers
- ☑ All elements of dates (except year)
- ☐ Health plan beneficiary numbers
- ☐ Vehicle identifiers and serial numbers, including license plate numbers
- ☐ Full face photographic images and any comparable images
- ☐ Biometric identifiers, including finger and voice prints
- ☑ All geographical subdivisions smaller than a State, including street address, city, county, precinct, zip code, except for the initial three digits of a zip code
- ☐ Any other unique identifying number, characteristic, or code (note this does not mean the unique code assigned by the investigator to code the data)
- ☐ None of the above will be collected

Will you collect health information as part of research procedures associated with this protocol?

Yes

Please be advised you are using Protected Health Information and need to have a process for Authorization. Both options below may be required for some protocols.

- ☑ Subjects will sign a HIPAA Authorization form
- ☑ Requesting a Waiver of HIPAA Authorization (45 CFR 160 and 45 CFR 164)

Based on previous answers, you must select "Requesting a Waiver of HIPAA Authorization".

Waiver of HIPAA

Please answer all four questions to submit your request for a Waiver of HIPAA Authorization.

1. Explain how the research presents no more than minimal risk to the subjects' privacy.
While the overall study does involve more than minimal risk (drug administration), we are asking for a waiver of HIPAA for screening purposes which do not present more than minimal risk. Participants give electronic and verbal consent during the 7091R screening process, during which PHI is obtained. When they come to NYSPI to complete additional screening, they sign and receive a hard copy of the HIPAA Authorization form.

2. Explain why the research could not be conducted without the Private Identifiable Information.
We need to gather information over the phone related to their identity (name) and age to confirm preliminary eligibility. Participants sign a hard copy of HIPAA when they come to NYSPI to complete additional screening procedures.

3. Describe your plan to destroy the identifiers as soon as possible consistent with the conduct of the research or provide a health or research justification for retaining the identifiers or explain how retention is required by law.
All data records containing identifying information will be kept in locked files and on password-protected computers. Only the principal investigator and other core study staff will have access to identifiable information, which will be maintained on site under lock and key. All computer data is stored without names or other identifiers. Participants will be identified only through a numerical code in all electronic databases. PHI data will be kept for 6 years (per HIPAA guidelines) and then destroyed.

4. Will the identifiable information be reused or disclosed to any other person or entity outside NKI/RFMH other than those identified in the protocol, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB?
No

Attach Consents

Attach Consents, Consent Waiver Scripts, Parental Permissions, or Assents Forms

8016.CF_4.14.23.pdf	Consent
Consent Quiz	Consent

Must be a Word Doc

- *NKI How to Use Consent Language and Template(s)*
- *NKI Sample Consent Language*
- *NKI Standard Consent Template*
- *NKI Clinical Trial Consent Template*
- *NKI Assent Template*
- *NKI Consent Form Addendum Template*
- *NKI Phone Screening Guidance*
- *NKI Information Sheet for Waiver of Documentation of Consent*

Attach HIPAA

Must be a Word Doc

- *OMH/OPWDD HIPAA Authorization Template*
- *OMH/OPWDD HIPAA Parental Permission Authorization Template*
- *PP1 Notice of Privacy Practice*

HIPAA	HIPAA Authorization

Future use, Privacy, and Confidentiality

Are there plans to use the data and/or specimens collected for this current study in future research?
No

Confidentiality

Describe the plan for protecting the confidentiality of the data/specimens collected as part of this research.

There are many ways to protect subject confidentiality. Common method includes the assignment of a code number to the data/specimen, separated from the subjects' name or other identifying information.

Methods to protect confidentiality. Potential participants divulge information that is sensitive and may have adverse social consequences if released. This would include information released to insurance companies, health care agencies, family members, or made public in any way. This study is NIH-funded and thus automatically covered by a Certificate of Confidentiality, and procedures for protecting confidentiality of records will be followed. Specifically, all data records containing identifying information will be kept in locked files and on password-protected computers. Only the principal investigator and other core study staff will have access to identifiable information, which will be maintained on site under lock and key. All computer data is stored without names or other identifiers. Participants will be identified only through a numerical code in all electronic databases.
Following the NYSPI Remote Communications Guidance, confidentiality of remote communication is protected using secure, HIPAA-compliant telecommunication (e.g., Webex, Zoom, Facetime, telephone, or Google Voice) in combination with digital data collection procedures (through remote access to secure NYSPI systems). Additionally, all email communications will be encrypted.

Provide a description of the protections in place to safeguard participants' privacy while information is being collected, such as where will you conduct the consent process or collect data from interaction with the subject.
Minimizing risks associated with the study procedures--

Prospective participants will be recruited into the study through advertisements in local newspapers and an online classifieds site (CraigsList). All advertisements will be approved by our IRB prior to posting. Prospective participants will first receive a general consent form covering the screening and evaluation processes. Next, they will be evaluated by a study team consisting of research psychologists, nurses, and physicians. These screening assessments include: a standard psychiatric evaluation that includes an abridged Structured Clinical Interview for DSM-V Disorders (SCID-V), mental status examination, physical examination, and laboratory assessment. The study principal investigator and research physician will review each participant's history, mental status exam, and medical evaluation and determine whether the participant is eligible and competent to consent. Individuals who meet inclusion/exclusion criteria will be offered participation in the proposed investigation. The study PI and research physician will describe the study in detail, including study procedures, and possible risks and benefits of participation. Participants may sign the consent form only after reading it, having any questions answered, and being given a copy to keep. Participants will be scheduled for laboratory sessions after they complete this screening and informed consent process. We will also strictly implement our inclusion/exclusion criteria. Participants are excluded if they have severe psychiatric illness (e.g. mood disorder with functional impairment or suicide risk, schizophrenia) that might interfere with their ability to participate in the study or their capacity to provide informed consent; current use of amphetamines, cocaine, antihistamines, tricyclic antidepressants, barbiturates, benzodiazepines, opioids, other Rx or over-the-counter analgesics, or muscle relaxants are exclusionary because of the risk of concomitant side effects and study confounds (participants will be instructed not to use any of these drugs during the study period); meeting DSM-V criteria for a Substance Use Disorder for any drugs other than caffeine, nicotine, or cannabis; pregnancy is exclusionary due to the possible effects of cannabis on fetal development; the evaluating psychiatrist reviews all medical assessments along with medical history; history of an allergic reaction to cannabis. These criteria are designed not only to optimize study findings but also to minimize risk to participants. In addition to strict implementation of our inclusion/exclusion criteria, we will also take vital signs regularly throughout the duration of the study in order to maintain the safety and well-being of participants, specifically during the repeated pain challenges. During the inpatient stay, participants will have vital signs taken each morning (Table 2). Vital signs will also be taken before and after each pain assessment, as well as one additional time halfway through the duration of each CPT. On pain testing days we will also measure vital signs before the second cannabis administration of the day, as well as in the late afternoon once participants have completed that day's tasks (Table 2). If any participant experiences sustained increased blood pressure response to the CPT (systolic > 180 or diastolic > 110 for over 120 seconds) we will stop the CPT immediately in order to protect the participant. We will confer with a staff internist and continue to monitor the participant's vital signs every 30 minutes until the episode has resolved or until the staff internist has determined that acute medical intervention is indicated. In addition to closely monitoring vital signs during pain assessments, we will also ensure that there is significant recovery time between sets of repeated pain challenges. Staff members will be present with participants for the entirety of the pain assessments, including time in between assessments. This allows for constant monitoring of the participant's safety. Minimizing COVID-19 exposure risk. To reduce the risk of participants being exposed to COVID-19 during study participation, participants will be informed of all NYSPI's safety guidelines prior to study enrollment. If enrolled, participants will be strictly required to follow these safety guidelines while on-site. Additionally, research staff will strictly follow all safety guidelines while interacting with study participants.

Minimizing COVID-19 exposure risk--
To reduce the risk of participants being exposed to COVID-19 during study participation, participants will be informed of all NYSPI's safety guidelines prior to study enrollment. If enrolled, participants will be strictly required to follow these safety guidelines while on-site. Additionally, research staff will strictly follow all safety guidelines while interacting with study participants.

Will data/specimens be shared with anyone outside of NKI/RFMH?
No

Risk, Benefit, Compensation, & Alternatives

Risks

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study.

Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes. Include data on risks that have been encountered in past studies. Related to past studies, list all risks that occurred.

For Clinical Trials, Adverse Events from animal or human studies should be detailed or referenced in this section.

Cannabis administration

Participants will be administered one of two smoked cannabis conditions (active: 4.91%THC:2.98% CBD or placebo: <0.01%THC:CBD) during the active phase of the laboratory study. The most frequently reported adverse experiences associated with cannabis administration include changes in the pattern of heart beats, heart pounding, paranoia, slurred speech, loss of coordination, dizziness, shakiness, clumsiness, lightheadedness, confusion, faintness, concentration difficulties, dependence, restlessness, sleepiness, fatigue, itching, sweating, flushing, paleness, headache, dry mouth, stomach upset, and increased appetite.

Cannabis abstinence/withdrawal

During the inactive phase of the laboratory study, participants will be administered inactive smoked cannabis (<0.01% THC:CBD); this abrupt cessation of cannabis use can induce cannabis withdrawal. The most frequently reported adverse experiences associated with cannabis withdrawal are anxiety, mood changes, aggression, anger, irritability, nervousness, shakiness/tremors, restlessness, difficulty sleeping, decreased appetite, weight loss, abdominal pain, sweating, fever, chills, and headache.

Describe all measures implemented to minimize risks of harm (precautions, safeguards).
Risks of cannabis administration, abstinence, and withdrawal:

This study administers cannabis and has daily cannabis users undergo abrupt cessation of use. The effects of cannabis administration and the possible onset of cannabis withdrawal symptoms is described to participants before study onset. As part of our informed consent procedures, we describe the effects of cannabis administration (e.g., dry mouth, increased heart rate) and the potential consequences of abrupt cannabis abstinence (e.g., irritability, difficulty sleeping, decreased appetite). We also list these symptoms in the consent form. All side effects will be reported to the study investigator to discuss severity. Expected effects of cannabis administration or abstinence will be recorded but not reported as AEs unless deemed severe (Grade 3 or above). Any symptomology that is considered clinically significant or that was not described in the consent form will be documented in the adverse event log in the study regulatory binder. Adverse event reporting will follow the guidelines set forth by the IRB of record and NYSPI and will be recorded in the AE log.

The Cold Pressor Test (CPT):

The CPT requires the use of warm (36.5-37.5ºC/97.7-99.5ºF) and cold water (3.5-4.5ºC/38.3- 40.1ºF). While the temperature of the warm water is characteristic of bath water, the cold water causes redness and slight discomfort due to the nature of the assessment. Pain resulting from this assessment is acute, resolves within minutes, and leaves no lasting effects. The CPT is also associated with cardiovascular changes that include elevations on heart rate and blood pressure. Participant's heart rate and blood pressure will be taken before each CPT begins, halfway through each CPT session, and once each assessment is complete. The CPT will be performed eight times during seven of the inpatient study days, as well as once during the training session.

Quantitative Sensory Testing – Thermal Temporal Summation (QST-TTS):

QST-TTS requires the use of a thermode that begins heat stimulation at 32.0°C/89.6°F, increases at a rate of 1°C/s, and reaches a temperature of 46.5°C/115.7°C, remaining constant for 120 seconds. The total duration of stimulation is 135 seconds. While the nature of the task is to produce slight pain, the heating element is designed not to exceed safe temperatures that could result in skin damage and has an automatic shut-off feature. Patients will be evaluated during screening for any indication of nerve damage using von Frey filaments. Potential risks during QST-TTS are minimal, which include a burn akin to a sunburn. These happen extremely infrequently (<1%) and are not expected to occur at the temperatures utilized in this proposal. Vital signs will be taken before and after each assay. The QST-TTS will be performed eight times during seven of the inpatient study days, as well as once during the training session. Repeated QST-TTS is currently being conducted in two other studies within our group (#8016 and #8058), and no issues have occurred to date. Further, an investigator (Dr. Peggy Compton, University of Pennsylvania) with experience in repeated QST-TTS is a consultant on this project and has provided input

that given sufficient time (10 minutes) between repetitions of testing, participants will be protected against adverse reactions. Dr. Compton did not report any known contraindications of QST-TTS.

Repeated Pain Challenges:

Both the CPT and the QST-TTS will be performed eight times per day during seven of the inpatient days and once during the training session. Repeated pain challenges may temporarily increase blood pressure and heart rate and cause some discomfort in the case of the CPT. The QST-TTS has not been found to have any cardiovascular risks. Participants will be given sufficient time to recover between sets of repeated pain challenges.

Inpatient Research Designs:

The problems associated with living in the inpatient laboratory have been minimal in the participants we have tested in similar types of protocols. We describe at length the isolation, boredom, and inactivity before volunteers sign the consent form, and thus far, have not encountered problems in this area. Of course, participants are free to leave the study at any time, and care is taken to be sure that this option is understood.

Pregnancy:

Female participants must be non-pregnant to be included in the study. A plasma pregnancy test will be performed during screening and a urine pregnancy test will be conducted immediately prior to conducting each training
visit and laboratory visit.

COVID-19 Exposure:

Participants will be required to travel to NYSPI for outpatient sessions and will reside in the Cannabis Research Laboratory's Residential Laboratory in cohorts of two-four as part of their participation in this study. Participants will be informed of the potential risk of contracting COVID-19 from infected individuals while traveling to our laboratory in the study consent form and subsequent consent discussions with research staff

COVID-19 Test:

A nurse or physician will put a cotton swab up both sides of the nose and move it around for about 15 seconds. Participants are informed of possible discomfort associated with collecting a nasal sample.

Benefits

Provide the current benefit to subjects involved in this study and the potential benefit that this study offers for future research.

This description should be based on accrued data from related studies that have been completed. There should be a rational description of why such benefits are expected based on current knowledge. If there is no direct benefit to subjects of this project, make an explicit statement that there is no direct benefit.

This study will not provide any direct benefits to participants.

Subject Compensation

Will there be any compensation provided to subjects?
Yes

Please describe any compensation provided to subjects and justification for such compensation.
Compensation is provided for participants' time and effort in the study. Participants are paid a $40 bonus for each inpatient day if they complete the entire study. They are paid for each component prior to move in at that visit, and then will be paid half of their total remaining compensation at move-out and asked to come back one week later to receive the second half of their remaining total. Participants who arrive on move-in day ready and eligible to participate but who were not selected (due to over- enrollment) will receive $75 and be sent home.

1. Phone screen/Qualtrics, $ 20.00 (2 visits)= $40.00
2. in-person screening, $ 26.00
3. Training Visit, $50.00
4. Move in, $40.00
5. Inpatient Day (base), $50.00 (14 inpatient days)= $700.00
6. Inpatient Day (bonus), (14 inpatient days) = $700.00
7. Move out $20.00

Are subjects reimbursed for travel or other expenses?
Yes

Please describe any reimbursement for travel or any other expenses.
If you will compensate subjects $600 or more annually, you must include language in the consent form.
In addition to study compensation, participants will be given $6 for subway/bus fare for visits that require travel to NYSPI (factored into the payment for in-person screening, move-in, move-out).

Total compensation:$1,576.00

Alternatives to Participation

Describe the Alternatives to Study Participation
An important alternative is also not to participate in this research.
This is not a treatment study for cannabis use or for pain; data are being collected for research purposes. If participants are interested in treatment for their cannabis use, we will give them a referral to a treatment program.

Participation is Voluntary:
Participation in this project is voluntary. If potential participants decide not to participate or if they later decide to stop participating, they will not lose any benefits to which they are otherwise entitled. A decision to not participate or withdraw participation will not affect current or future treatment at the New York State Psychiatric Institute or Columbia University. Participants will be informed of any new findings or risks that arise that may affect their willingness to continue in this study. The investigator may also decide that their participation should be discontinued under certain circumstances (e.g., following an adverse event).

Data Management, Data Monitoring, Reportable Events, and Incidental Findings

Data Management

Include in this section the plan for acquiring data (both electronic and hard copy).

For example, if you are obtaining data from a record system, what is your plan for obtaining access to the system (if applicable) or receiving the data from an administrator of that system (if applicable). Be sure to include plans for all data, including paper and pencil survey.

We will be using secure web-based central electronic data capture systems (e.g., Acquire EDC, REDCap, etc.) for automated data collection. This electronic data capture systems ensure the privacy and security of the data collected by meeting the Good Clinical Practice (GCP) guidelines and the following applicable Federal Regulations-Health Information Portability and Accountability Act (HIPAA), Federal Information Security Management Act (FISMA), and Food and Drug Administration (FDA) 21CFR Part 11. Access to this database is limited to research approved personnel, who have received training on handling human subjects' data and systems training. The principal investigator or a qualified data management staff member will train research assistants on how to properly enter data into and review and resolve data queries in the electronic data capture systems. Study data such as subjective-effects, self administration, and other objective and subjective ratings will be entered into Research Electronic Data Capture (REDCap)—a secure, HIPAA-compliant, FDA 21 CFR Part 11 compliant, web-based application.

All virtual participant assessments and videoconferencing sessions will be hosted via Zoom or WebEx—secure, HIPAA-compliant video conferencing recommended by NYSPI (using institutional accounts only). For participants with email access, any study related information that contains PHI will be sent via encrypted email. The Principal Investigator will identify a single qualified research member who will have access to and manage the REDCap database, under the PIs supervision. If significant changes are made to the data management plan we will submit those as protocol amendments.

Study team members that have regular access to records and data include research assistants, the study coordinator, sub-investigators, the principal investigator, and study physicians when necessary. As previously mentioned, all physical subject records including screening folders and case report forms are securely stored in locked cabinets within room 3602 on site, and any electronic data is password protected on the SURC server that can only be accessed by the study staff.

Data Storage

Describe the storage location (for both electronic or hard copy files), length of time stored, and plan for destruction.

If storing data on devices (including laptops, workstations, flash drives, backup tapes, etc.), please attest that the devices are encrypted and protected with a strong password (Example: "Hardcopy records will not be maintained for this study; Electronic records will be maintained on the password protected file on the HIPAA drive"). Be sure to include who has access to these devices.

Data storage for this study involves both hard copy and electronic versions. Electronic-captured data, such as Inquisit tasks, occur on ResLab laptop where participant responses are then transferred to a hard drive. Once on the hard drive, all data is exported to our lab's server. Any forms of hard copy data are transcribed by two different study personnel onto password protected files and maintained onto the lab's server. All devices and hard drives are encrypted and protected with a strong password.

After the transfer onto the server, hard copy data is stored in locked storage cabinets within the lab (room 3602). Only study personnel (PIs, Research Assistants, and study staff) have access to the electronic and hard copy files of data, due to restricted password or key access.

Specimen Storage and Management

Managing and Storing Specimens

Include in this section the plan for acquiring specimens.

For example, will specimens be collected by the research team, or will they be received in another way? Please detail this process.

Blood samples are collected by the research team during screening as a part of routine lab work to confirm participants are healthy prior to enrollment. During the screening process, the staff collect urine as part of the screening protocol (7091R). The collected samples are promptly disposed of and are not stored as LabCorp destroys samples in the second section.

Describe the storage location, length of time stored, and plan for destruction.

Blood samples are sent out to LabCorp and are not stored on site at NYSPI. Blood samples are destroyed by LabCorp after bloodwork is run.

Data Monitoring

All studies should have a plan for monitoring study data. The need for a formal committee or a designated study team monitor is based on the risk of the study design.

Is there a Data Monitoring Committee (DMC), Data Safety Monitoring Board (DSMB), or other monitoring entity for this study?
Yes

Detail who comprises this committee:
Caroline Arout, PhD (PI)
Jeanne Manubay, MD (study physician)

Detail what will be monitored:
Both the principal investigator and study physician will provide ongoing review of the data and safety of the study participants during daily communication with the research staff, as well as at weekly lab meetings. In addition, ongoing and annual review of any serious adverse events (SAEs) are monitored by the Institutional Review Board (IRB) of the New York State Psychiatric Institute, the National Institute on Drug Abuse (NIDA), and the Food and Drug Administration (FDA). All AEs reported by participants or observed by the research staff will be individually listed on our Adverse Event Form (AEF). The signs and symptoms, time of onset, duration, severity, medical intervention, follow-up procedures, and suspected relationship to study drug will be reported. Any AE (clinical signs and symptoms or laboratory test results) associated with cannabis or oxycodone administration will be documented by the study physician and nurse. If any SAEs occur during this study, they will be reported to the IRB, NIDA, and the FDA, which will review the SAE report and suggest appropriate actions and, if necessary, study modifications. The Principal Investigator and study physician will determine whether the seriousness of the event warrants removal of any participant from the study.

A. Data Entry and Checking

1. Every data EXCEL sheet has a tab for a data progression log; any time anything is entered or edited, it is noted in the progression log including the date, the initials of person handling the data and what section of the data was entered.
2. There are two approaches for assuring data integrity:
-- a. Some data is entered independently by two individuals, e.g., double-entered. The data is entered twice into identical tabs of a spreadsheet and then a formula is used to compare the tabs and search for differences. e first and second entries are done by two different people. See below for instructions on how to create compare formula.

--b. Some data is entered by one individual and a second person then double checks it for accuracy. See below for the double-checking procedure

Detail the frequency of review:
Formal monitoring of participant records will occur monthly, where the PI will review all records of 10% of study charts. Participant issues will also be discussed weekly with the research team at our lab meeting.

Reportable Events

Events that occur in research that may represent unanticipated problems involving risks to subjects or others should be promptly reported using the Event report form within 10 days of the investigator's or research staff member's learning of the event, except for these circumstances:

1. If the event is related to a fatality that is related to study participation or possibly related to study participation, the incident should be report to the IRB within two (2) business days of discovery of the event.

2. Events resulting in temporary or permanent interruption of study activities by the investigator, sponsor, or DSMB (Data Safety and Monitoring Board) to avoid potential harm to subjects should be reported within IRB within two (2) business days.

Incidental and Unexpected Findings

Incidental findings are observations of potential clinical significance unexpectedly discovered in research participants and unrelated to the purpose or variables of the study.

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research.

In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider.

In cases where the participant could possibly benefit medically or otherwise from study screening or other information, the results of screening, research participation, research tests, etc., will be shared with subjects and/or their primary care provider upon consent from the participant.

Data Analysis and References

Statistical/Data Analysis Plan

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses.

Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analysis (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis.

All data analyses will be based on models using repeated measures analysis of variance (RM-ANOVA) analyzed as a function of cannabis condition (active vs. inactive) and day (Day 1-15), and sets of planned comparisons, calculated with SPSS or SUPERANOVA statistical packages. The planned comparisons, outlined below, are a priori, and designed to test the specific hypothesis for each aim. Tests of differences for all comparisons will be based on F-statistics with degrees of freedom corrected, depending on the observed within-subject correlation of the measures, using the method of Geiser and Greenhouse or Huynh and Feldt. Results will be considered statistically significant at $p < 0.05$, using 2-tailed tests. Distribution of demographic variables (ethnicity, age, sex) will be described in terms of means, standard deviations, proportions, and 95% confidence intervals, where appropriate.

Please list all references.

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Funding

Are there any changes being made to the Funding or COI information?

Yes

Please indicate the origin of the project. (Who conceived of and leads the development of the project, regardless of funding.). Select all that apply.

- ☑ Investigator initiated (Investigator(s) developed protocol)
- ☐ Industry (Pharmaceutical, Device, etc.) (Industry developed protocol)
- ☐ Federal Agency (NIH, DOD, etc.)
- ☐ Foundation Funding
- ☐ Internal Funding
- ☐ Other

Please state whether you receive Federal, State, Pharmaceutical Company, or other (be specific) funding for the conduct of this project.

If you receive no funds, please list "No Funding" under "Funding Type."

Funding Type	Project Title in Grant	Business Office	Source	Source Identifier.... (Grant #)	Subcontract	Subcontract Institution	Funding Start Date	Funding Expiration Date
No funding	No Funding	NONE	No Funding	No Funding	Subcontract from:	No Funding		12/31/2023
Industry	Effects of Repeated High-Cannabidiol Cannabis Administration on Experimental Pain and Abuse Liability in Humans	RFMH	Alkermes	No grant number		No subcontract	01/01/2020	12/31/2023

If applicable, please indicate the which institution the grant or contract is funded through.

☐ Not Applicable
☑ RFMH
☐ NYU
☐ CU
☐ Other

Does any member of the study team have a Conflict of Interest?

Conflict of Interest *is defined as a situation in which financial (funds paid outside of a sponsored project agreement), non-financial or other personal considerations compromise, or have the appearance of compromising, an individual's professional judgment in proposing, conducting, supervising, or reporting research (i.e., consulting, speaking, or acting as a Sponsor or Board member, etc).*

If you are unsure about a COI please select "yes" and complete the following section.

No

Supporting Attachments

Please include any support attachments. NYSPI Investigators must upload their ancillary checklist and all supporting approvals for the checklist, as well as the SRMP. If you are submitting an NHSR determination request, ancillary checklist and SRMP is not required.

Some items that may need to be attached include sample data collection sheets, Sponsor Brochure/Protocol

Must be a Word Doc

8016 Continuing review form	Annual Review Form
7091R (Evaluation protocol) consent form	Consent
IND amendment to add 8016	FDA Correspondence
IND ownership transfer correspondence 2023	FDA Correspondence
Grant application	Grant
8016 Ancillary Review Checklist and Attestation_CA.11.20.24 (1).pdf	Misc/Other
8016 Area Lead Approval	Misc/Other
8016 Greenlight letter	Misc/Other
8016 Safety Review outcome letter	Misc/Other
DMP approval	Misc/Other
FCOI	Misc/Other
Letter of support from inpatient unit	Misc/Other
7091R (Evaluation protocol) PSF	Protocol

Upload all currently approved forms, even if they are no longer in use (i.e. you are in data analysis)

This should include the last approved consent/assent forms, HIPAA docs, scripts, advertisements, SSRP, Location/Funding/Personnel Supplements, Letters of Support, etc.

8016_Ad_6.13.23_Final (1).pdf	Advertisement
Consent quiz	Consent
Consent Form	Consent
8016 updated HIPAA_3.7.23.pdf	HIPAA Authorization
AE Log	Misc/Other
PD Log	Misc/Other
Table 2 (referenced in procedures)	Misc/Other
(PSF_2024) Effects of Repeated High_Cannabidiol Cannabis Administration on Experimental Pain and.pdf	Protocol