PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Kevin P. Hill, M.D., M.H.S.

PROTOCOL TITLE
Combination of Dronabinol and Clonidine for Cannabis Dependence in Patients with Schizophrenia

FUNDING
NARSAD Young Investigator Award

VERSION DATE
9/10/15

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Aim 1: Assess the relationship of treatment with the combination of dronabinol and clonidine or placebo on cannabis use patterns in cannabis-dependent subjects with an Axis 1 psychiatric disorder.

Aim 2: Assess the relationship of treatment with the combination of dronabinol and clonidine or placebo on cannabis withdrawal symptoms in cannabis-dependent subjects with an Axis 1 psychiatric disorder.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

People with mental illness are more likely than healthy people to abuse cannabis (Kovasznay et al. 1997). Although it is unclear why this is true, patients with mental illness may use cannabis to alleviate unpleasant affective symptoms (Gregg

et al. 2007). Cannabis dependence may trigger unpleasant symptoms and worsen the outcome of the disease in this group (Linszen et al. 1994). Unfortunately, effective medications for cannabis-dependent individuals with an Axis I psychiatric disorder have not been identified. Combinations of medications may offer advantages not available with monotherapy. Haney et al. (2008) showed that the combination of THC and the α2-adrenergic receptor agonist lofexidine decreased symptoms of cannabis withdrawal, craving, and relapse in a human lab study of daily cannabis smokers. Although lofexidine is not approved for use by the United States Food and Drug Administration (FDA), clonidine, another α2- adrenergic receptor agonist, is FDA-approved and commonly used in clinical practice. Therefore, we build upon this exciting finding by proposing a pilot study of the combination of THC, specifically Dronabinol (Marinol®, Solvay Pharmaceuticals, Marietta, GA, or generic, specific manufacturer to be determined) which is an orally-active cannabinoid agonist that is approved by the FDA for the treatment of anorexia associated with weight loss in patients with AIDS and nausea and vomiting associated with cancer chemotherapy (Marinol® product information); and clonidine as a treatment for cannabis dependence in schizophrenic individuals.

Our study may provide initial evidence for a readily available, effective treatment for cannabis dependence in subjects with mental illness. This combination treatment may reduce cannabis withdrawal symptoms that function as an obstacle for subjects with mental illness trying to stop using cannabis.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

8.1. Overview

We will conduct a Stage 1 pilot feasibility study at McLean Hospital to develop a combination of medication protocol to treat cannabis dependence in subjects with schizophrenia, schizoaffective, or any Axis I disorder. In a randomized, double-blind, placebo-controlled trial, 18 cannabis-dependent male and female subjects ages 18-45 with an Axis I psychiatric disorder will receive medical management (MM) over a 10-week period, with half receiving treatment with the combination of dronabinol and clonidine and half receiving placebo. Subjects will receive

either the combination of dronabinol 5 mg by mouth three times daily and clonidine 0.1 mg my mouth twice daily or placebo in addition to MM over a 10-week treatment period. A follow-up visit after treatment at week 14 will evaluate the durability of treatment effects on drug use and psychosocial outcomes. Primary outcomes will include self-report of cannabis smoking and results of quantitative urine drug screens for cannabis. We also will assess cannabis withdrawal symptoms, including mood and craving. Mixed models ANOVA will be used to analyze the data.

8.2. Participants

Subjects are cannabis-dependent male and female volunteers with mental illness ages 18-45 years old and will be recruited via newspaper advertisements, word of mouth, web-based advertisements, and the Psychotic Division Clinical Research Core (Protocol # 2009-P-002016)

A total of 18 cannabis-dependent volunteers with any Axis I disorder (9 men, 9 women) will serve as subjects. Factoring in a potential 20% dropout of those who actually begin the protocol, we estimate that 7-8 people will probably be exposed to dronabinol in this pilot study. In order to meet the target sample of 18 completers (8 subjects per group), we expect to recruit about 50 subjects to initially prescreen, with about 35 who will then sign the informed consent. Of those who sign the informed consent form, 14-18 will probably end up being randomized.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

8.2.1. Study Procedure

8.2.1.a. Recruitment and Intake.

Interested individuals will respond to advertisements by leaving a message (first name and call back number only) in the BPRL recruiting voice mailbox. Research assistants will call them back with 24 to 48 hours and conduct an initial phone screen that takes about 15 minutes. It will cover basic inclusion and exclusion criteria, as well as a brief description of the study to determine if the person is interested in participating. If the volunteer is appropriate and agrees to participate, they will be invited to come to the BPRL for a physical and psychiatric evaluation (SCID). Treatment alternatives will also be offered to the prospective participant if they decide not to participate or are not eligible for participation.

Psychiatric Evaluation. A Structured Clinical Interview- DSM-IV (SCID) will be performed by a qualified research assistant, clinical psychologist, or psychiatrist.

Physical Exam. The medical exam will be performed by a physician. A blood draw and12-

lead ECG will be performed by a research assistant; results will be interpreted by a study physician.

Safety Monitoring. The subjects will undergo the following screening procedures: a) Detailed history of cannabis use; b) Review of DSM-IV criteria for cannabis dependence; c) Review of DSM-IV criteria for schizophrenia and schizoaffective disorder; d) Medical history and concomitant medication record; e) Physical examination; f) Laboratory screen that includes CBC, electrolytes, and BUN/creatinine; g) Urine measurement of THC; h) Urinalysis and urine pregnancy test for women; i) 12-lead electrocardiograph (ECG); j) urine toxicology screen; k) blood alcohol testing; l) Positive and Negative Syndrome Scale (PANSS); m) Columbia Suicide Severity Rating Scale (C-SSRS). The study physician will perform a physical examination and obtain an ECG at baseline and at 14 weeks. Laboratory data (urinalysis, blood chemistries, complete blood count, electrolytes, and liver function tests) will be done at baseline, 5, 10, and 14 weeks as well. Given that according to its labeling, dronabinol should not be taken with alcohol, sedatives, hypnotics, or other psychoactive substances because they could potentiate the central nervous system effects of dronabinol, urine toxicology and blood alcohol testing will be done weekly along with the twice weekly quantitative THC urine screens during treatment. Women of childbearing potential will have urine pregnancy tests weekly each time a urine sample is given in addition to pregnancy tests at 4 and 8 weeks during treatment; women who become pregnant will have their medication discontinued and will be referred to an obstetrician; like all subjects, they will still be followed for research visits. Suicide risk will be assessed by the physician at each MM visit.

Study Restrictions

Subjects will be instructed to keep us informed of any medications initiated after their enrollment in the study. Subjects will be reminded of the potential for additive CNS depression resulting from concomitant use of dronabinol and alcohol, opioid analgesics, benzodiazepines, and barbiturates. They will be warned initially of these potential additive effects during the informed consent process. Participants will be warned not to drive, operate machinery, or engage in any hazardous activity while receiving dronabinol. Subjects will also be informed that clonidine may cause drowsiness, dizziness, or lightheadedness associated with orthostatic hypotension. These effects may be worse if taken with alcohol or other medications that can cause drowsiness.

Subjects will be warned not to abruptly stop taking clonidine.

Subjects will also be informed that data on the use of antipsychotic medications and dronabinol and/or clonidine is lacking. Due to the potential for sedation and possible hypotension in subjects taking these medications together, we will monitor carefully for these symptoms while educating subjects about these possible side effects.

8.2.1.b. Informed consent. Eligible subjects will complete standard consent documentation. Prior to the volunteer being asked any question about his/her health, the volunteer will be given a consent form to read. The research assistant will go over it in detail with the volunteer. After a physician investigator answers any questions the volunteer may have concerning the study, he/she will be asked to provide their informed consent to the licensed physician investigator. If enrolled in the study, consent to communicate with their other clinicians will be obtained. Clinicians will be notified of their patients' enrollment in the study, thus allowing them to carefully monitor for changes in mood while they are undergoing treatment to stop use of cannabis.

8.2.1.c. Randomization. Research staff will stratify subjects according to their self-reported frequency of cannabis use in the past 30 days: 1) daily use; and 2) non-daily use. The stratification procedure will guard against the possibility that one of the

experimental conditions (i.e., dronabinol-clonidine or placebo) will be overrepresented by daily users, while non-daily users will predominantly be randomized into the other condition.

8.2.1.d. Availability and Flow of Subjects into Treatment. We plan to screen 50subjects in the course of 20 months to achieve our desired sample size.

8.2.1.e. Study Visits. Following eligibility for the study (as determined by the baseline-1 visit), subjects will come to the laboratory for a baseline-2 visit to complete research assessments, provide a urine sample, and begin daily diaries and Actiwatch (see Section 8.5.2.a.)Subjects will then come to the clinic twice a week during the study medication treatment phase. One visit will include a medical visit (dispensing of pills and Medical Management; see Sections 8.3.1.b, 8.3.2) and research assessments, including a urine screen (see Section 8.5.2.a and Table 8.2). The other visit will consist only of a urine screen (see Section 8.5.2.a). After the 10-week treatment period, participants will have a follow-up assessment visit at 14 weeks. . Subjects will also come in once weekly during weeks 11, 12, and 13 following the 10-week treatment period to provide a urine sample, and hand in daily diaries/actiwatch.

Subjects will be randomized to receive either dronabinol and clonidine or placebo. Dr. Hill or the research assistants will present 7 day prescriptions to the McLean pharmacy and the subject will receive blister packs containing 1 week of medication or placebo, separated into daily doses. Subjects will be asked to return unused pills at each weekly medical visit; study staff will then perform a pill count for the study record. All groups will receive capsules following the same schedule: 2 capsules three times daily for 10 weeks. Each capsule will contain either dronabinol, clonidine, or placebo. Subjects in the dronabinol-clonidine group will take 5 mg of dronabinol three times daily for 10 weeks (between 7:00-9:00 AM, 3:00-5:00 PM and 9:00-11:00 PM). Subjects in this group will also take clonidine 0.1 mg po bid (between 7:00-9:00 AM and 9:00-11:00PM) for 8 weeks, followed by a taper to clonidine 0.1 mg po qhs for the last 2 weeks of the protocol. Subjects will be assessed for side effects prior to each dosing increase and the study physician will decide if increasing the dose as scheduled is appropriate. See Table 1 for a schedule of study visits.

Table 1 Schedule of Measures

Measure	Baseline 1 and 2	Weekly Monitoring Week 1		Follow-up Weeks 5,10	Week 14
Diagnostic Assessment					
1. Structured Clinical Interview for DSM-IV[a]	X B1				
Drug and Alcohol Assessment					
2. Quantitative Urine Toxicological Analysis[b]	XB1,B2	X[b]	X	X	X
3. Addiction Severity Index	XB2		X	X	X
4. Drug and Alcohol Use Questionnaire	XB1				
5. Weekly Drug and Alcohol Use Inventory	XB1,B2	X	X	X	X
6. Marijuana Goals Questionnaire	XB1				
7. Marijuana Craving Questionnaire	XB1,B2	X	X	X	X
8. Marijuana Withdrawal Checklist	XB1,B2	X	X	X	X
Mood and Impulsivity Assessment					
9. Quick Inventory of Depressive Symptomatology	XB1,B2			X	X
10. Barratt Impulsiveness Scale	XB1,B2			X	X
11. Beck Anxiety Inventory	XB1,B2			X	X
Medical & Safety Assessment					
12. Physical examination	XB1				X
13. ECG	XB1				X
14. Urine pregnancy test	XB1,B2	X	X	X	X
15. Vital Signs[c]	XB1,B2	X	X	X	X
16. Positive and Negative Syndrome Scale	XB1,B2				
17. Behavioral Activity Rating Scale	XB1		X		
18. Laboratory tests[d]	XB1			X	X
19. Adverse Events & Side Effects	XB1,B2	X	X	X	X
20. Columbia Suicide Severity	XB1	X	X	X	X
21. Marijuana Perceptions of Risk and Experiences Questionnaire (MPRE) Rating Scale	XB1			X	X

[a]Full SCID at baseline

[b]Twice a week during treatment

[c]Vital Signs include pulse and blood pressure (sitting and standing)

[d]Tests include urinalysis, liver function tests, electrolytes, complete blood count, & blood chemistries

B1= Baseline 1 (screening visit)

B2=Baseline 2 (baseline 2 visit post screen for subjects who qualify for participation before treatment begins)

8.2.1.f. Clinical Emergencies. If a subject is intoxicated, the subject will be evaluated medically, sent home in a taxi when safe, and the appointment re-scheduled. If a subject experiences a problem that requires clinical intervention during the course of the study (e.g., mania, suicidal ideation, or dangerous intoxication), we will evaluate the situation medically, make an appropriate recommendation, and help the subject to implement this plan. This could involve hospitalization at McLean, referral to the hospital's outpatient program, or other medical or psychiatric treatment, as clinically appropriate.

8.2.1.g. Subject Payments. Volunteers will receive a $50 honorarium for attending the initial assessment interview, $25 for baseline-2 visit, and $50 for follow-up visits at 5, 10, and 14 weeks. They may earn $25 for each urine sample given on a non-MM day in the first 5 weeks of the treatment and $30 for each urine sample given on a non-MM day during the last 5 weeks of treatment. They will be compensated $50 for the W eek 1 monitoring visit and $30 for each of three actiwatch diary UA visits at wks 11,12, and 13. They may also receive a bonus of up to $100 for successful completion of all diaries. They may earn a total of $740 for their participation in the study. Medication will be free.

A payment request will be submitted for each part of the study they finish. The research assistants will arrange for payment to be sent via mail to the subjects.

8.3. Treatment. (Dr. Hill has been granted IND 108676 by the FDA to use this medication combination in this protocol.)

Dronabinol (Marinol®, Solvay Pharmaceuticals, Marietta, GA) is an orally-active cannabinoid agonist that is approved by the FDA for the treatment of anorexia associated with weight loss in patients with AIDS and nausea and vomiting associated with cancer chemotherapy (Marinol® product information). Dronabinol will be titrated to 5 mg three times daily in the dronabinol-clonidine group. Doses of up to 90 mg of dronabinol daily have been well-tolerated in studies of its effects upon cannabis- dependent individuals (Levin and Kleber 2008, Haney et al. 2008, Haney et al. 2004, Budney et al. 2007).

Clonidine (Catapres®, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) is α_2- adrenergic agonist that is approved by the FDA for the treatment of hypertension (Catapres® product information). Clonidine will be administered at 0.1 mg twice daily in the dronabinol-clonidine group prior to a 2-week taper to clonidine 0.1 mg po qhs.

Placebo will be vegetable capsules (Gallipot, Inc., St. Paul, MN) double encapsulated into 00 capsules. Physicians are ACLS-trained and have access to a "crash cart" located in the laboratory. All study personnel are basic life support-trained and have practiced assisting a physician in the event of an emergency.

8.3.1.c. Dose Adjustment.

Subjects who experience uncomfortable side effects (e.g., drowsiness or vertigo) may have their dose lowered from 2 capsules three times a day to 2 capsules twice daily by eliminating the middle dose of the day; a subject receiving active medication, for example, could then have a dronabinol dose reduction to 10 mg of dronabinol daily. If this leads to fewer side effects, the study physician will ask if the subject is willing to try the full dose again. If not, or if the subject tries the full dose again and is unable to tolerate it, the subject will be maintained on the lower dose. If a subject cannot tolerate 2 capsules twice per day, the medication will be discontinued, and the subject will be tapered off of the Clonidine, but the subject will continue to be followed for research visits. Similarly, we will monitor for potential cardiovascular side effects resulting from clonidine pharmacotherapy. At each medical management visit, we will assess vital signs and ask the subject about symptoms of orthostatic hypotension, such as dizziness when rising to stand from a seated position, blurry vision, or weakness. If subjects describe these symptoms without meeting exclusionary blood pressure criteria, we will hold the third set of capsules to see if this leads to fewer side effects, the study physician will ask if the subject is willing to try the full dose again. If not, or if the subject tries the full dose again and is unable to tolerate it, the subject will be maintained on the lower dose. If a subject cannot tolerate 2 capsules twice per day, the medication will be discontinued, but the subject will continue to be followed for research visits.

8.3.2. Medical Management Visits.

8.3.2.a. Weekly Visits with the Study Physician. Subjects will be seen weekly during treatment by the study physician for medical visits. In addition to dispensing the study medication, the physician will utilize Medical Management (MM) (Pettinati et al 2004), a manualized treatment that was used in the NIAAA COMBINE Study. MM was derived from empirically-tested manualized therapies (Carroll and O'Malley 1996, Mason and Goodman 1997) that were originally designed to approximate a primary care approach to the treatment of alcohol dependence. The treatment is delivered by a medical professional who monitors medication side effects, provides strategies to increase medication adherence (Volpicelli et al. 1997), and supports abstinence. The initial 40-60 minute session includes reviewing the cannabis dependence diagnosis and negative consequences from smoking marijuana, recommending abstinence, providing medication information, and offering strategies to enhance medication adherence. In subsequent 15-25 minute visits, recent substance use, overall functioning, medication adherence, and side effects are discussed. Session structure varies according to drug use status and medication adherence. If a subject is not adherent to the medication regimen, the clinician evaluates the reasons and helps the subject devise plans to enhance medication adherence. Subjects who use cannabis are given common-sense behavioral recommendations, such as avoiding parties where marijuana will be present. Presence and severity of side effects will be obtained through a standard. Adverse Events Checklist as well as the "Frequency and Intensity of

Side Effects Rating/Global Report of Side Effects Burden" (Wisniewski et al. 1997), a 2-minute questionnaire that assesses the frequency, intensity, and level of burden of side effects. Medication adherence will be assessed in several ways, as outlined below in Section 8.6. These sessions will be audiotaped and a sample will be rated by a senior clinician in order to ensure fidelity to the MM process.

8.5. Research Measures.
See Table 8.2 for the schedule of assessments.

8.5.1. Diagnostic Assessment. To make the diagnoses of cannabis dependence, the Structured Clinical Interview for DSM-IV (SCID) (First 1996) will be used.

8.5.2. Drug and Alcohol Use Assessment.
8.5.2.a. Urine Screens. The primary outcome measure will be cannabis use, as measured by twice-weekly quantitative urine screens during treatment. . Quantative urine screens will also be measured during weeks 11, 12, 13, and 14 following the 10- week treatment period. Cannabis is a particularly challenging drug of abuse for measuring outcome because of the false-positive urine screens that can occur as the result of long-term accumulation of cannabis metabolites. In an attempt to avoid false-positive results, we will obtain 2 supervised urine samples weekly: 1 at the medical visit and 1 on another day, ordinarily with 3-4 days separation from the clinical visits (e.g., Monday-Thursday, Tuesday-Friday, or Monday-Friday); this should maximize the time frame covered by our urine screens. We will send the urine samples to Quest Diagnostics Laboratory (Cambridge, MA, a NIDA-certified laboratory), where the urines will be screened by immunoassay for the THC metabolite 11-nor-carboxy-Δ 9- tetrahydrocannabinol (THC-COOH) as well as other drugs of abuse. Urine creatinine concentrations will also be measured to assess urine concentration. The threshold for detection of THC-COOH will be 20 ng/ml. Samples positive for this metabolite will undergo further analysis by gas chromatography-mass spectroscopy to obtain quantitative THC-COOH concentration; we will then calculate the ratio of this metabolite to urine creatinine concentration. We will adopt the method of Heustis and Cone (1998) to differentiate new marijuana use from residual drug excretion as a result of previous use; these recommendations are based on their controlled clinical studies of urinary excretion profiles of creatinine and marijuana metabolites following marijuana administration in humans. We will label a urine negative (i.e., abstinent from cannabis) if 1) the ratio of THC-COOH to creatinine in the urine does not increase by >50% from the ratio obtained in the previous urine screen, and 2) the subject also reports using no cannabis since the previous urine test.

8.5.2.b. Self-Report. We will use 3 methods of self-report in an effort to determine the most appropriate and effective method for use in this population. An ActiWatch-Score will be determined via compact, wrist-worn, battery-operated activity monitors that are excellent devices for monitoring multiple drug use, drug craving, and sleep/wake activity (Licata et al., under review). We will provide subjects with a packet of 1 page, self- addressed, prepaid postage Daily Diary pages which subjects will be asked to fill out between 7:00 and 9:00 a.m. each day and.hand them in during their weekly visits. The diary consists of a series of questions about marijuana and other drug use as well as eating habits. During weeks 11, 12, and 13 subjects will have 1 weekly Diary/Actiwatch visit to hand in their daily diaries, , provide a urine sample, and have their Actiwatch data downloaded. During the weekly visits, we plan to collect cannabis use data using the Timeline Follow Back (TLFB) (Sobel and Sobel 1992) protocol that was developed for alcohol.

8.5.2.c. Other Drug and Alcohol Use Assessment. Severity of cannabis and other substance use and its associated problems will be assessed at baseline and weeks 5,10, and 14 with the Addiction Severity Index (ASI, 5th edition) (McLellan et al. 1992), a widely-used and independently-validated interview that measures the severity of problems in 7 areas of functioning that are frequently

affected in patients with SUDs: drug use, alcohol use, employment, legal status, medical condition, social functioning, and psychological status. In addition to our primary focus on marijuana use (urine screens plus days of use), we will examine other substance use (using urine screens plus days of other substance use). We will use this method to determine the number of days of marijuana use and of any substance use (and conversely, days of abstinence). We will examine ASI composite scores as secondary measures of substance use outcome. We will also use the self-administered Drug and Alcohol Use Questionnaire. This measure, administered at baseline, addresses the context of lifetime and recent drug and alcohol use, as well as sociodemographic data. At each treatment visit, patients will complete a brief Weekly Drug and Alcohol Use Inventory, indicating their number of days using marijuana, other drugs, and alcohol during the previous week. The Marijuana Goals Questionnaire (Griffin et al. 1989) is a brief questionnaire administered at baseline to assess treatment goals, specifically, whether a subject is seeking abstinence or reduction in marijuana use. A 12-item self-administered questionnaire, the Marijuana Craving Questionnaire, will be used to assess craving at baseline and weekly during treatment and at the 14-week follow-up visit (Heishman et al. 2009). A short form of the Marijuana Withdrawal Checklist will be used to assess withdrawal symptoms at baseline and weekly during treatment and at the 14-week follow-up visit (Budney et al. 1999). If there is a discrepancy among results obtained by these methods of substance use assessment, we will meet with the subject and have a conversation about their substance use. After the conversation, we will use our clinical judgment to determine the level of use that we believe is most accurate for that subject. A 6-page questionnaire that we created titled Marijuana Perceptions of Risk and Experiences (MPRE), will be distributed at baseline, and once during weeks 5, 10 and 14 to assess each participant's perceptions of cannabis risk/harm and his or her motivations to quit/continue using cannabis throughout the course of treatment.

8.5.3. Mood and Impulsivity Assessments. We will monitor subjects' mood and impulsivity throughout the study using 3 assessments. The Beck Anxiety Inventory (BAI) is a 21-item self-report measure that can be used to assess the severity of anxiety. The Quick Inventory of Depressive Symptomatology (QIDS-SR) is a short self-report questionnaire for depressive symptoms used successfully in the STAR*D project. The Barratt Impulsiveness Scale (BIS-11) is a commonly used tool to measure impulsivity in various neuropsychological disorders as well as in substance abuse. Three dimensions can be assessed using this scale, which include Cognitive Impulsivity, Motor Impulsivity, and Non-planning Impulsivity.

8.6. Medication Adherence Assessment. The proposed studies involve chronic administration of medication given under double-blind conditions. Three methods of medication adherence will be used as multiple methods are preferred (Weiss 2004): 1) pill counts will be made; 2) subjects will record when they take their capsules on the ActiWatch-Score device; 3) urinary riboflavin levels (a 25 mg dose will be given with each dose of medication) will be measured using a UV spectrophotometer. If there is a discrepancy among results obtained by these methods, we will meet with the subject and have a conversation about their medication adherence. After the conversation, we will use our clinical judgment to determine the level of adherence that we believe is most accurate for that subject.

8.8. Data Management

All data collected will be de-identified with subject ID numbers and used for research purposes only. Written records will be kept in a locked file cabinet in a locked office. They will be destroyed after 7 years. Computerized data files will also be de- identified with subject ID numbers and kept in a password protected file on a password protected computer.

8.9. Statistical Analysis

The primary data analysis will be an intent-to-treat analysis, which includes all randomized subjects. Of note, every attempt will be made to continue assessing subjects even if they drop out of treatment. In addition, we will replicate all analyses with the completers only. The primary and

secondary outcome variables are intended to explore various aspects of response to therapy and to help define a clinically meaningful response. The primary outcome measures, Actiwatch-scores, daily diaries, TLFB self- report data, in addition to quantitative urinary THC metabolites, have been chosen for their ability to indicate daily use of cannabis by relying on self-report of use. Specifically, for assessing the effect of dronabinol and clonidine on cannabis use patterns, we propose to use the generalized estimating equations (GEE) approach to longitudinal analysis, appropriately accounting for the positive correlation among repeated urine screen assessments within the same individual. Analyses of secondary substance use outcomes will focus on the number of days of cannabis use and of any substance use (and conversely, days of abstinence) during treatment and post-treatment follow-up. In addition, we will also examine the ASI Drug and Alcohol composite scores. Frequency of days of cannabis use (and any substance use and days of abstinence) will be analyzed via a log-linear (or Poisson) regression model, controlling for pre-treatment frequency of days of cannabis use. Although log- linear regression methods are considered appropriate for the analysis of count or frequency data, in many biomedical applications, count data have variability that far exceeds that predicted by the Poisson distribution; we expect that days of cannabis use (and any substance use and days of abstinence) will not be an exception. Linear mixed effects models will be used to examine the effect of treatment group on changes in the ASI Drug and Alcohol composite scores during treatment and post-treatment follow-up assessments (as determined by the group-by-time interaction in the linear mixed effects regression models). The linear mixed effects model will include random intercepts and slopes to appropriately account for correlation among repeated measures and heterogeneity of variance over time; the model will be fit using PROC MIXED in SAS.

In secondary analyses of mood outcomes, mood episodes will be assessed during treatment and post-treatment follow-up,using the QIDS-SR, , BAI, and BIS-11; ; changes in risk of mood episodes during treatment and post-treatment follow-up assessments will be analyzed via a logistic regression model (similar to the logistic model above) that will be fit using the GEE approach (as implemented in PROC GENMOD in SAS) to account for correlation among repeated binary outcomes on the same individual. To examine the effect of dronabinol and clonidine on changes in risk for mood episodes during treatment and post-treatment follow-up, the logistic regression model will include the effects of treatment condition and the baseline measure of the outcome.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

The standard of care for cannabis dependence is psychotherapy; our treatment centers upon a medication.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Care will be taken to minimize risk. In addition to carefully screening prior to enrollment, we have scheduled regular laboratory visits during which we will carefully monitor response to medication or placebo with respect to side effects and changes in mood.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of

improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

8.3.1.b. Safety Monitoring.

In order to monitor potential side effects from the initial dose of dronabinol, subjects will be observed at the laboratory facility for 4 hours following the following the first dose of the day in week 1. Subjects will come into the Behavioral Psychopharmacology Research Laboratory for monitoring by a research assistant and a study physician. This observation period is follows the SAMHSA guidelines for induction of buprenorphine, another agonist pharmacotherapy (CSAT 2004). Subjects will remain in the natural settings laboratory for a minimum of 2 hours and a maximum of 6 hours while having vital signs taken every 30 minutes. Subjects will be allowed to leave the facility by cab after being cleared by a study physician. Subjects will be allowed to leave the facility if they have 1) pulse rate greater than or equal to 50 beats per minute or less than or equal to 135 beats per minute; 2) blood pressure less than or equal to 140/90 and greater than or equal to 90/50; and 3) Behavioral Activity Rating Scale (BARS) score of less than 6. If pulse is decreasing, blood pressure is increasing, or BARS is increasing at the 2-hour assessment, the subject will remain an addition 30 minutes until the trend for these parameters is in the correct direction and the subject meets criteria for medical clearance.

During the 10-week treatment period, subjects will be seen for a MM visit and for urine screen visit. Medication compliance and side effects will be monitored at all visits. The initial visit in week 1 will include a monitored administration of medication described above. Subjects will have follow-up visits at 5, 10 and 14 weeks that will include a urine screen, blood sampling for laboratory testing, as well as evaluation for medication side effects.

Stopping Criteria. New psychotic symptoms thought to be related to dronabinol administration that are present at any pre-dose assessment or that remain present at the end of a 2-hour monitoring period will result in stopping of dronabinol. Clonidine stopping criteria include bradycardia less than or equal to 50 bpm, supine blood pressure of less than or equal to 100/65, a seated blood pressure of less than or equal to 90/60, or orthostatic change of >20 systolic or >10 diastolic on standing, at screening or any pre-dose assessment, or symptoms attributable to low BP (i.e. lightheadedness or dizziness on standing). Adverse events or side effects resulting from administration of either dronabinol or clonidine that persist beyond 7 days will warrant a call to the subjects PCP if they have one, and a decision will be made by the study physician about possible continued participation. If the subject is stopped, they will be followed for follow-up visits only.

Clinically significant lab abnormalities (liver function tests ≥3X normal, for example) will be rechecked immediately and, if determined to be clinically significant by the study physician, the subject will be removed from the protocol and followed for follow-up visits only. Worsening psychotic symptoms that predated study medication will warrant a call to the subject's psychiatrist and possible removal from the protocol if the patient is thought to be unstable by either the outpatient psychiatrist or the study physician. Similarly, suicidal ideation will warrant contact with the outpatient psychiatrist and possible removal from the protocol. Suicidal ideation with a plan will result in immediate removal from the protocol and the subject will be escorted by staff to the Psychiatric Emergency Room.

Events that may lead to stopping of the study include physiological side effects attributed to study medication such as seizure, psychomimetic reactions (hallucinations, paranoia, etc.), suicide, or other deaths. If any one of these occurs in 2 subjects, we will consider stopping the study if those effects can reasonably be associated with study participation. Due to the potential of dronabinol to lower seizure threshold, we will halt the study if 2 subjects have seizures during their participation. If any one besides seizure occurs in 3 subjects, we will halt the study.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for

research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

The screening process and questions related to a subject's psychiatric history may cause discomfort. While dronabinol is FDA-approved for treatment of nausea related to cancer chemotherapy, subjects may experience side effects when taking nabilone, including hallucinations, paranoia, extreme fear; fast heart rate; feeling light-headed, fainting; or unusual thoughts or behavior. Less serious side effects are also possible including drowsiness, euphoria, weakness, lack of coordination; depression, anxiety, confusion, dry mouth; headache, trouble concentrating; insomnia. Subjects will also be informed that clonidine may cause drowsiness, dizziness, or lightheadedness associated with orthostatic hypotension. These effects may be worse if taken with alcohol or other medications that can cause drowsiness. Subjects will be warned not to abruptly stop taking clonidine.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

At the completion of this study, we hope to have improved our understanding of the relationship of the combination of dronabinol and clonidine on cannabis use.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

Men, women, and minorities will all be recruited. Pregnant women and children will be excluded in part due to the lack of data on the safety of dronabinol in these groups.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Proficiency in English is necessary for a long-term treatment study that includes 10 MM sessions and ensures that the participants can properly convey any subtle side effects that relate to their safe participation in this study.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

9. Human Subjects and Recruitment Strategies:

9.1. Sample Size: In order to meet the target sample of 18, We plan to initially prescreen 50 subjects, with about 35 signing the informed consent, ages 18-45 in the course of 20 months to achieve our desired sample size.

9.2. Advertising: Subjects will be recruited via websites, newspaper advertisements, flyers on campus, word-of-mouth, and the Psychotic Division Clinical Research Core. We will not specifically recruit subjects from particular patient units at McLean. Subjects may not be inpatients at McLean at the time of their participation in the study.

9.3. Inclusion criteria

Inclusion:

1) Age range 18-45 years; 2) DSM-IV diagnosis of cannabis dependence, based on the Structured Clinical Interview for DSM-IV (SCID); 3) DSM-IV diagnosis of an Axis I Disorder on the Structured Clinical Interview for DSM-IV (SCID); 4) express a desire to quit cannabis use within the next 30 days; 4) have used cannabis on 20 days within the past 30 days (i.e., an average of 5 day per week); 5) identify cannabis as their primary drug of abuse; 6) stable on antipsychotic medication for 1 month; 7) for women of childbearing age, a negative pregnancy test at screening with agreement to use adequate contraception to prevent pregnancy and monthly pregnancy tests; 8) consent for us to communicate with their prescribing clinician if one exists; 9) furnish the names of 2 locators, who would assist study staff in locating them during the study period; 10) live close enough to McLean Hospital to attend study visits; 11) plan to stay in the Boston area for the next 3 months; and 12) are willing and able to sign informed consent.

9.4. Exclusion criteria

1) Current diagnosis of other drug or alcohol dependence (excluding nicotine); 2) significant cardiac disease as indicated by history or suspected by abnormal ECG or history of cardiac symptoms; 3) Positive and Negative Syndrome Scale (PANSS) subscale for positive symptoms of psychosis item > 3 (moderate) at baseline evaluation; 4) current medical condition that could prevent regular study attendance; 5) liver function tests >3 times the upper limit of normal range; 6) history of seizure disorder or history of head trauma or CNS insult that could predispose the subject to seizures; 7) taking Clozapine, Wellbutrin, Mirtazapine, and/or Guanfacine; 8) current suicidal risk; 9) bradycardia less than or equal to 50 bpm, supine blood pressure of less than or equal to 100/65, a seated blood pressure of less than or equal to 90/60, or orthostatic change of >20 systolic or >10 diastolic on standing, at screening or any pre-dose assessment, or symptoms attributable to low BP (i.e. lightheadedness or dizziness on standing); 10) mental retardation or organic mental disorder; 11) currently in a residential treatment setting in which substance use is monitored and restricted, since the restricted access to drugs could represent an important confounding variable; 12) pregnant, nursing, or, if a woman of childbearing potential, not using a form of birth control judged by the investigator to be effective; 13) concomitant treatment with opioid analgesics, sedative hypnotics, or other known CNS depressants; 14) known hypersensitivity to

cannabinoids or sesame oil or clonidine; 15) disease of the gastrointestinal system, liver, or kidneys that may impede metabolism or excretion of dronabinol; 16) inability to read or write in English that would hinder their ability to follow study procedures; 17) history of seizures or a family history of seizures.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Subject Payments. Volunteers will receive a $50 honorarium for attending the initial assessment interview, $25 for baseline-2 visit, and $50 for follow-up visits at 5, 10, and 14 weeks. They may earn $25 for each urine sample given on a non-MM day in the first 5 weeks of the treatment and $30 for each urine sample given on a non-MM day during the last 5 weeks of treatment. They will be compensated $50 for the Week 1 monitoring visit and $30 for each of three actiwatch diary UA visits at weeks 11, 12, and 13. They may also receive a bonus of up to $100 for successful completion of all diaries. They may earn a total of $740 for their participation in the study. Medication will be free.

A payment request will be submitted for each part of the study they finish. The research assistants will arrange for payment to be sent via mail to the subjects.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Informed consent. Eligible subjects will complete standard consent documentation. Prior to the volunteer being asked any question about his/her health, the volunteer will be given a consent form to read. The research assistant will go over it in detail with the volunteer. After a physician answers any questions the volunteer may have concerning the study, he/she will be asked to provide their informed consent. If enrolled in the study, consent to communicate with their other clinicians will be obtained. Clinicians will be notified of their patients' enrollment in the study, thus allowing them to carefully monitor for changes in

mood while they are undergoing treatment to stop use of cannabis.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aicipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Safety Monitoring. Dronabinol and clonidine both have been shown to have favorable safety profiles; they have been well-tolerated in several clinical trials and few adverse events have been reported. Nonetheless, we will monitor safety through the standardized methods described above in the MM visits. We will have a low threshold for obtaining additional medical workup during the study if the subject reports medical symptoms. If a subject has a clinically significant laboratory or other medical abnormality that cannot be attributed to another cause, the subject's medication will be discontinued and the subject will be followed for research visits.

As discussed above in Section 8.2.i.a, the study physician will perform a physical examination and obtain an ECG at baseline and at 24 weeks. Laboratory data (urinalysis, blood chemistries, complete blood count, electrolytes, and liver function tests) will be done at baseline and 5, 10, and 14 weeks as well. Women of childbearing potential will have urine pregnancy tests at 4, 8, and 14 weeks during the study; women who become pregnant will have their medication discontinued and will be referred to an obstetrician; like all subjects, they will still be followed for research visits.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include

the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

The Principal Investigator assumes responsibility for ensuring informed consent, data management, and the detection and reporting of adverse events. In general, the data to be reviewed will include screening data, baseline data, efficacy data, safety data, quality assurance data, accrual status including projections, and any other data that will help in the assessment of the effectiveness of the clinical trial.

The risk associated with participating in this study is moderate. Dronabinol has been established as a safe treatment for nausea associated with cancer chemotherapy. Clonidine is a safe treatment for hypertension. Consequently, serious side effects associated with this treatment are not expected. There will be on-call medical coverage to respond to any adverse events throughout the clinical trial. The Principal Investigator will conduct a review of all adverse events and determine the attribution and grade of severity of the adverse event by using the following scales:

Attribution of Risk Categories:

Definite: Adverse event(s) will clearly be related to investigational agent(s) or other intervention
Probable: Adverse event(s) will likely be related to investigational agent(s)
Possible: Adverse event(s) may be related to investigational agent(s)
Unlikely: Adverse event(s) will doubtfully be related to investigational agent(s)
Unrelated: Adverse event(s) will clearly not be related to the investigational agents(s)

Grades of Risk:

0: No adverse event or within normal limits
1: Mild adverse event
2: Moderate adverse event
3: Severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect
4: Life-threatening or disabling adverse event
5: Fatal adverse event

Serious adverse events (SAEs) include any untoward medical occurrence that at any dose results in death or the immediate risk of death, hospitalization or the prolonging of an existing hospitalization, persistent or significant disability/incapacity or a congenital anomaly/birth defect. Subjects will be terminated from participation if the investigator feels that subjects' health or well-being may be threatened by continuation in the study. Serious unanticipated adverse events will be reported within 48 hours to the Partners IRB and NIDA. We will directly report to the FDA whenever their magnitude or frequency exceeds expectations. The principal investigator will evaluate the adverse event and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol are required. In addition, he will conduct a review of all adverse events at least semi-annually, and he will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example,

specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The research assistants will be responsible for day-to-day monitoring of the validity and integrity of the data. Dr. Hill will meet with the research assistants to discuss data monitoring on a monthly basis and will sample subject data folders monthly as well.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

Data Management

All data collected will be de-identified with subject ID numbers and used for research purposes only. Written records will be kept in a locked file cabinet in a locked office. They will be destroyed after 7 years. Computerized data files will also be de-identified with subject ID numbers and kept in a password protected file on a password protected computer.

To help us protect patient privacy, we have obtained a Certificate of Confidentiality From the National Institutes of Health. We can use this Certificate to legally refuse to disclose information that may identify a patient in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

Not applicable.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

Not applicable.