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
Cannabidiol Pharmacotherapy for Adults with Cannabis Use Disorder

FUNDING
Partial funding from Dr. Hill's Sundry Account, medication and placebo provided by GW Pharmaceuticals.

VERSION DATE
3/1/17

SPECIFIC AIMS

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

Aim 1: Assess the relationship of treatment with either cannabidiol or placebo, when added to medical management, on cannabis use patterns.

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Aim 2: Assess the relationship of treatment with either cannabidiol or placebo, when added to medical management, on cannabis withdrawal and cannabis craving.

Aim 3: Assess the relationship of treatment with either cannabidiol or placebo, when added to medical management, on other factors that may affect treatment outcome, such as depressive symptoms, anxiety symptoms, memory, and cigarette use.

BACKGROUND AND SIGNIFICANCE

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

In the era of decriminalization of marijuana, medical marijuana, and legalization of marijuana, marijuana use has become a global concern. More people in the world abuse cannabis than any other illicit drug. (WHO 2014) There are over 18 million people in the United States that have used cannabis in the past month. (SAMSHA 2013) While only a fraction of those users develop problems with addiction, a small fraction of a large number can be a very large number—in this case there are millions of people in the United States and around the world that are addicted to cannabis and therefore require treatment. (Bobb and Hill 2014) In addition, the Monitoring the Future study conducted annually in the United States has shown that marijuana use among adolescents has continued to rise while, chillingly, their perception of marijuana's risk has declined. (Johnston et al. 2014) In the face of these concerning statistics and

trends, there are no FDA-approved pharmacotherapies for cannabis use disorder despite a critical need.

Epidiolex® is a promising cannabinoid that modulates multiple signaling systems, making it an intriguing possible pharmacotherapy for a wide range of medical problems, including addiction. (Russo 2011; Thomas et al. 2007) In this Stage 1 feasibility study, treatment-seeking individuals ages 18-45 with cannabis use disorder will receive either Epidiolex up to 800 mg daily or matching placebo in addition to medical management over a 6-week treatment period. This pilot study, if successful, would provide the impetus for a National Institutes of Health R01 grant proposal to conduct a larger clinical trial for this treatment. Dr. Hill has conducted several clinical trials of treatments for cannabis use disorder and he currently is funded by a NIDA K99/R00 Pathway to Independence Award during which he has completed a pilot study of nabilone as a pharmacotherapy for cannabis use disorder and he is conducting a second larger clinical trial of nabilone pharmacotherapy as a part of this grant. Two ongoing trials of cannabinoids for cannabis use disorder and another previously completed trial for participants with cannabis use disorder show that Dr. Hill can obtain investigational new drug (IND) approvals from the FDA, recruit, and carry out these trials at McLean.

We aim to determine Epidiolex's promise as a pharmacotherapy for cannabis use disorder. We hypothesize that Epidiolex, when added to medical management, will result in greater reductions in marijuana use compared to placebo as measured by our 2 primary outcome measures: 1) quantitative THC levels and 2) self-report by Timeline Follow Back. Secondary outcome measures will include treatment retention, patient satisfaction, cannabis withdrawal, cannabis craving, depressive symptoms, anxiety symptoms, compliance, and cigarette use.

Dr. Hill applied for and was granted IND 127385 by the FDA to study cannabidiol as a pharmacotherapy for cannabis use disorder.

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 begin to evaluate Epidiolex as a pharmacotherapy for adults with cannabis use disorder. In a randomized, double-blind, placebo-controlled trial, cannabis-dependent subjects ages 18-65 will receive medical management over a 6-week period, with half receiving Epidiolex treatment and half receiving placebo. Participants will receive either up to 800 mg Epidiolex or placebo over a 6-week treatment period. Following treatment completion, participants will have a follow-up visit at 10 and 14 weeks. Primary outcomes will include self-report of cannabis smoking and results of quantitative urine drug screens for cannabis. Secondary outcome measures will include treatment retention, patient satisfaction, cannabis withdrawal, cannabis craving, depressive

symptoms, anxiety symptoms, compliance, and cigarette use. Mixed models ANOVA will be used to analyze the data.

8.2. Participants

A total of 60 cannabis-dependent volunteers (30 men, 30 women) will serve as subjects. In order to meet the target sample of 30 completers (15 subjects per group), we expect to screen about 60 subjects and have about 60 sign the informed consent form. Of those who sign the informed consent form, 24-30 will probably end up being randomized.

All subjects must use a medically approved method of contraception to participate in the study (e.g. birth control pills, IUD, condoms). Both men and women must agree to use reliable contraceptive precautions for the duration of the study and 3 months following discontinuation. This includes condoms or other forms of birth control that are recommended and/or prescribed by the participant's physician, such as oral contraceptive pills, diaphragm, or implantable medication. During the physical, the physician will ensure that the potential volunteer is using adequate methods to prevent pregnancy.

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

8. 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.

The initial assessment interview will be done by a research assistant and the study physician and take about 3 hours. Volunteers will first be asked to sign the informed consent (see *8.2.1.b*). Once they have agreed to participate, they will undergo a comprehensive evaluation that will include medical, psychiatric, and drug use histories as well as physical, psychiatric, and laboratory examinations. The study will be explained and an intake package, including all Drug and Alcohol and Mood and Impulsivity Assessments (see Table 8.1), will be administered. More specifically, the participants will undergo the following screening procedures:a) Detailed history of cannabis use; b) Review of DSM-IV criteria for cannabis dependence; c) Medical history and concomitant medication record; d) Physical examination; e) Laboratory screen that includes CBC, electrolytes, and BUN/creatinine; f) Urine measurement of THC; g) Urinalysis and urine pregnancy test for women; h) 12-lead electrocardiograph (EKG) i) urine toxicology screen; j) blood alcohol testing; k) Columbia Suicide Severity Rating Scale (C-SSRS). Suicide risk will be assessed by the physician at each medical management visit.

8.2.1.b.Informed consent.

Eligible participants 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.

Participants will be stratified 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., CBD 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 100 participants in the course of 8 months to achieve our desired sample size.

8.2.1.e.Study Visits.

Participants will come to the clinic twice a week. One visit will include a medical visit (dispensing of medication 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 6-week treatment period, participants will have follow-up assessments visit at 10 and 14 weeks. During weeks 7-14, participants will have 1 weekly Diary/Actiwatch visit to hand in their daily diaries, have their Actiwatch data downloaded, and provide a urine sample.

8.2.1.f.Clinical Emergencies.

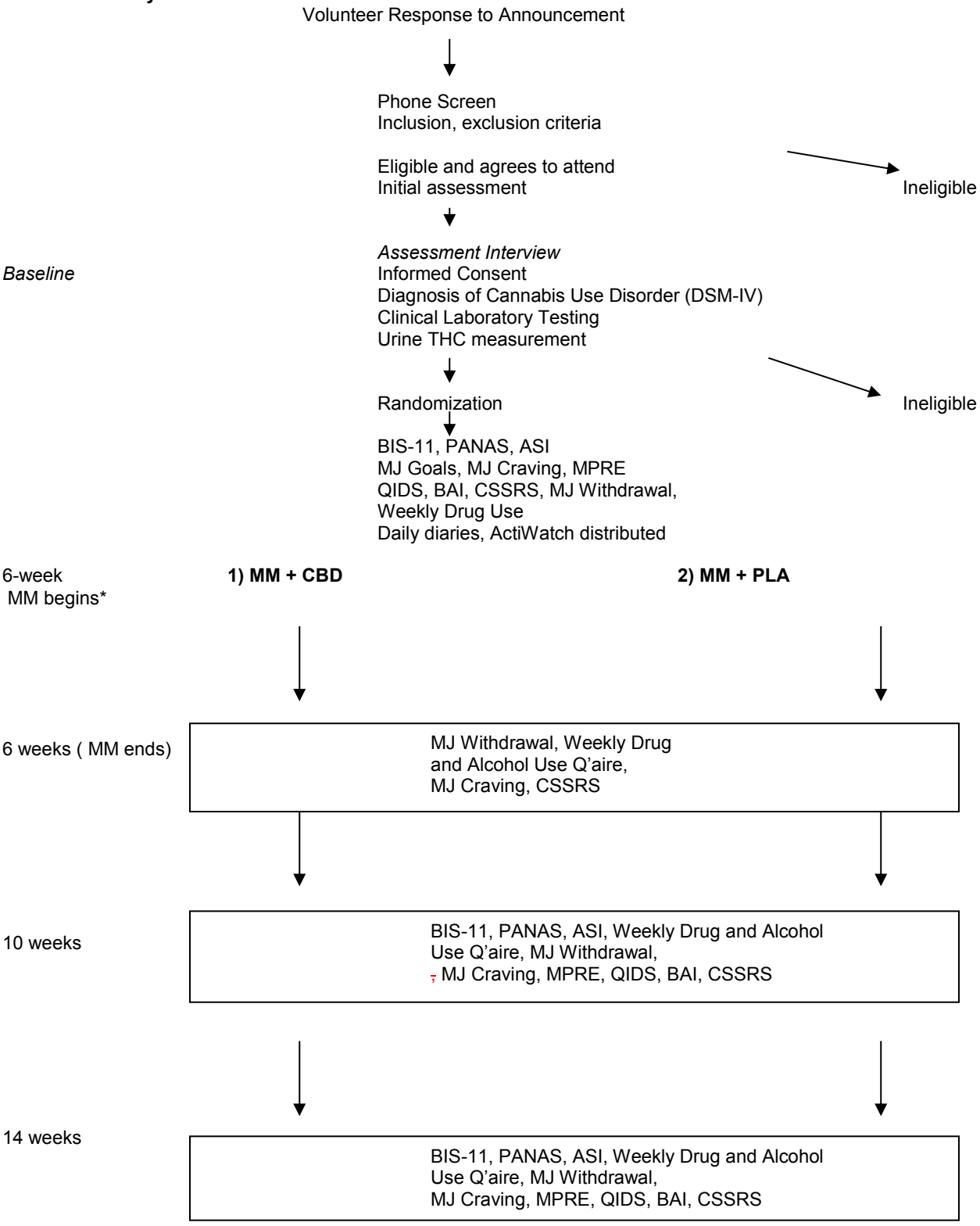
If a participant is intoxicated, the participant will be evaluated medically, sent home in a taxi when safe, and the appointment re-scheduled. If a participant experiences a problem that requires clinical intervention during the course of the study (e.g., mania, suicidal ideation, or dangerous intoxication), we will evaluate the situation medically, make an appropriate recommendation, and help the participant 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.Participant Payments.

Volunteers will receive a $50 honorarium for attending the initial assessment interview as well as $50 for the baseline visit. They may earn $20 for each urine sample given on a non-medical management day and $20 for attending each medical management visit. For each of the weekly 10-15 minute follow-up visits, subjects will receive $25. They may earn up to a total of $80 as a bonus for completing all of the

daily diaries. Subjects will receive up to $620 for their participation in the study. Medication will be free.

FIGURE 1. Study Schema



8.3. Treatment.

8.3.1Cannabidiol.

8.3.1.a.Rationale for Dose.

Cannabidiol (Epidiolex®, GW Pharmaceutical, UK), a cannabinoid that modulates multiple signaling systems, has yet to be approved in the United States. Both preclinical studies and clinical reports suggest that Epidiolex has promise as an addiction treatment (Russo 2011) perhaps in part due to its anti-anxiety effects or ability to produce extinction of conditioned place preference in animals. Epidiolex will be titrated to 800 mg daily in the Epidiolex group (although adjustments may be made to this maximum dose based upon participant's response – this pilot study will determine the optimum dose to be used in a larger clinical trial to follow this pilot). Although Epidiolex has not been studied as a pharmacotherapy for substance dependence, up to 1000 mg of Epidiolex has been well-tolerated in studies of its effectiveness as a treatment for treatment-refractory epilepsy.

8.3.1.b.Procedures for Dispensing Medication.

Participants will be randomized to receive either Epidiolex or placebo. Dr. Hill or the research assistants will present 7 day prescriptions to the McLean pharmacy and the participant will receive a container containing 1 week of medication liquid or placebo liquid. Participants will be asked to return unused medication at each weekly medical visit; study staff will then record the leftover amount for the study record. The Epidiolex titration dose in the first week by day will be 100 mg, 100 mg, 200 mg, 200 mg, 400 mg, 400 mg, 800 mg. Epidiolex is 100 mg per 1 ml of liquid, so participants will take 1 ml once daily for 100 mg (between 7PM-9PM), 1 ml twice daily for 200 mg (7AM-9AM, 7PM-9PM), 2 ml twice daily for 400 mg (7AM-9AM, 7PM-9PM), and 4 ml twice daily for 800 mg (7AM-9AM, 7PM-9PM). Participants will take 800 mg daily during weeks 2 through 5 and then reverse the titration in week 6. Participants 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.

*8.3.1.c.Dose Adjustment***.**

Subjects who experience uncomfortable side effects (e.g., drowsiness or vertigo) may have their dose lowered by 200 mg; a subject receiving active cannabidiol, for example, could then have a dose reduction from 8 ml of cannabidiol daily to 6 ml 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 the reduced daily dose, 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

Participants 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 participant is not adherent to the medication regimen, the clinician evaluates the reasons and helps the subject devise plans to enhance medication adherence. Participants who use cannabis are given common-sense behavioral recommendations, such as avoiding parties where marijuana will be present. 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.

8.3. Safety Monitoring.

Cannabidiol has been shown to have a favorable safety profile; it has been well-tolerated in several clinical trials and no adverse events have been reported. Nonetheless, we will monitor safety through the standardized methods described above in the medical management visits. We will have a low threshold for obtaining additional medical workup during the study if the subject reports medical symptoms. If a participant has a clinically significant laboratory or other medical abnormality that cannot be attributed to another cause, the participant's medication will be discontinued and the participant will be followed for research visits.

The subjects will undergo the following screening procedures: a) Detailed history of cannabis use; b) Review of DSM-IV criteria for cannabis dependence; c) Medical history and concomitant medication record; d) Physical examination; e) Laboratory screen that includes CBC, electrolytes, and BUN/creatinine; f) Urine measurement of THC; g) Urinalysis and urine pregnancy test for women; h) 12-lead electrocardiograph (ECG); i) urine toxicology screen; j) blood alcohol testing; k) 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, week 4 and at 14 weeks as well. Any subject found to have abnormal liver function tests during the screening visit will be excluded from the study (Note: Abnormal is defined as values outside the normal ranges for ALT, 7 to 55 units per liter, AST, 8 to 48 units per liter, and albumin, 3.5 to 5 grams per deciliter). If the patient's clinical presentation during the course of the study raises concerns of their liver function, an additional set of laboratory test will be obtained. If a subject's liver functions tests become elevated to great than or equal to five times the upper limit of normal during the

course of the study they will be withdrawn from the study drug. Women of childbearing potential will have urine pregnancy tests at the screening visit and monthly 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 medical management visit. If a subject expresses active suicidal ideation or other severe psychiatric symptoms, we will evaluate the situation medically, make an appropriate recommendation, and help the participant to implement this plan. They will be referred to an emergency room as deemed appropriate. If they require a structured treatment program in order to treat their suicidal ideation or psychiatric symptoms, they will be withdrawn from the study.

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. 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 management 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 participant 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 participants with a packet of 1 Daily Diary pages which participants will be asked to fill out between 7:00 and 9:00 a.m. each day and hand them in during their weekly visits to the lab. The diary consists of a series of questions about cannabis and other drug use as well as eating and sleeping habits. During the weekly visits, we plan to collect cannabis use data using the Timeline Followback(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 6, 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 cannabis 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 cannabis 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 participant is seeking abstinence or reduction in cannabis use. A 12-item self-administered questionnaire, the Marijuana Craving Questionnaire (MCQ), 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 (MWC) will be used to assess withdrawal symptoms at baseline and weekly during treatment and at the 10- and 14-week follow-up visits (Budney et al. 1999). If there is a discrepancy among results obtained by these methods of substance use assessment, we will meet with the participant 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 participant. A new 6-page questionnaire that we created, the Marijuana Perceptions of Risk and Experiences Questionnaire (MPRE), will be distributed at baseline, and once during weeks 6, 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 participants' mood 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 Positive and Negative Affect Scale(PANAS) is a 20-item self-report scale in which mood variables are rated by participants on a 1-5 scale. 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.

Table 8.1 Schedule of Measures

Measure	Baseline	Weekly	Weeks 10 &14
Diagnostic Assessment			
1. Structured Clinical Interview for DSM-IV[a]	X		
Drug and Alcohol Assessment			
2. Quantitative Urine Toxicological Analysis[b]	X	X[b]	X
3. Addiction Severity Index	X		X
4. Drug and Alcohol Use Questionnaire	X		
5. Weekly Drug and Alcohol Use Inventory	X	X	X
6. Marijuana Goals Questionnaire	X		
7. Marijuana Craving Questionnaire	X	X	X
8. Marijuana Withdrawal Checklist	X	X	X
9. Marijuana Perceptions of Risk and Experiences	X		X
Mood and Impulsivity Assessment			
10. Quick Inventory of Depressive Symptomatology	X		X
11. Beck Anxiety Inventory	X		X
12. Positive and Negative Affect Scale	X		X
13. Barratt Impulsiveness Scale	X		X
Medical & Safety Assessment (medical visits)			
14. Physical examination	X		Xf
15. ECG	X		Xf
16. Urine pregnancy testd	X		Xf
17. Laboratory tests[e]	X	Xe	Xf
18. Client Satisfaction Questionnaire			Xf
19. Adverse Events & Side Effects	X	X	X
20. Columbia Suicide Severity Rating Scale	X	X	X

[a]Full SCID at baseline
[b]Twice a week during treatment;
[c]Weeks 3 and 6 only
[d]Monthly after screening
[e]Tests include urinalysis, liver function tests, electrolytes, complete blood count, & blood chemistries (also tested during week 4)
f Week 14 only

8.6.Medication Adherence Assessment. The proposed studies involve chronic administration of medication given under double-blind conditions. Two methods of medication adherence will be used as multiple methods are preferred (Weiss 2004): 1) measurement of residual volume will be made; 2) participants will record when they take their doses on the ActiWatch-Score device; If there is a discrepancy among results obtained by these methods, we will meet with the participant 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 participant.

8.7. Data Management

All data collected will be de-identified with participant 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 participant ID numbers and kept in a password protected file on a password protected computer.

8.8. Statistical Analysis

The primary data analysis will be an intent-to-treat analysis, which includes all randomized participants. Of note, every attempt will be made to continue assessing participants 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 CBD 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, BAI, and PANAS; 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 CBD 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.

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.

Study procedures are described above.

The primary outcome measures will be quantitative urinary THC metabolites, Actiwatch-scores, daily diaries, and TLFB self-report data. In secondary analyses of mood outcomes, mood episodes will be assessed during treatment and post-treatment follow-up, using the QIDS, BAI, and PANAS.

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.

Safety Monitoring.

Cannabidiol has been shown to have a favorable safety profile; it has been well-tolerated in several clinical trials and no adverse events have been reported. Nonetheless, we will monitor safety through the standardized methods described above in the CBT visits. We will have a low threshold for obtaining additional medical workup during the study if the subject reports medical symptoms. If a participant has a clinically significant laboratory or other medical abnormality that cannot be attributed to another cause, the participant's medication will be discontinued and the participant will be followed for research visits.

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. Subjects may experience side effects when taking Epidiolex, including fatigue, drowsiness, and dizziness.

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 CBD 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 Epidiolex 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 4 medical management 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 30 completers, we expect to recruit 60 participants, ages 18-65 ~~45~~, and have approximately 60 of them sign the informed consent form.

9.2. Advertising:

Participants will be recruited via websites, newspaper advertisements, flyers on campus, and word-of-mouth. We will not specifically recruit participants from particular patient units at McLean. Participants may not be inpatients at McLean at the time of their participation in the study.

9.3. Inclusion criteria

1) Age range 18-65 ~~45~~ years; 2) DSM-IV diagnosis of cannabis dependence, based on the Structured Clinical Interview for DSM-IV (SCID); 3) express a desire to quit cannabis use within the next 30 days; 4) have used cannabis on ≥4 days within the past 30 days (i.e., an average of ≥1 day per week); 5) for women of childbearing age, a negative pregnancy test at screening with agreement to use adequate contraception to prevent pregnancy and monthly pregnancy tests; for men, contraception will be discussed at the beginning of the study with the study physician; 6) consent for us to communicate with their prescribing clinician; 7) furnish the names of 2 locators, who would assist study staff in locating them during the study period; 8) live close enough to McLean Hospital to attend study visits; 9) plan to stay in the Boston area for the next 3 months; and 10) are willing and able to sign informed consent.

9.4. Exclusion criteria

1) Current diagnosis of other drug or alcohol dependence (excluding nicotine); 2) recent (within 3 months) significant cardiac disease; 3) current serious psychiatric illness or history of psychosis, schizophrenia, bipolar type I disorder; 4) current medical condition (including significant laboratory abnormalities, such as abnormal liver function tests) that could prevent regular study attendance; 5) mental retardation or organic mental disorder; 6) acutely dangerous or suicidal behavior; 7) 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; 8) pregnant, nursing, or, if a woman of childbearing potential, not using a form of birth control judged by the investigator to be effective; 9) concomitant daily treatment with opioid analgesics, sedative hypnotics, or other known CNS depressants; 10) known

hypersensitivity to cannabinoids or sesame oil ; 11) disease of the gastrointestinal system, liver, or kidneys that may impede metabolism or excretion of CBD; 12) inability to read or write in English; 13) a history of seizures, head trauma or other history of CNS insult that could predispose the subject to seizures; 14) currently taking valproic acid, lamotrigine, or propranolol, medications metabolized by UGT1A9 or UGT2B7 enzymes (CBD may affect these UGT levels).

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

Participant Payments.

Volunteers will receive a $50 honorarium for attending the initial assessment interview as well as $50 for the baseline visit. They may earn $20 for each urine sample given on a non-medical management day and $20 for attending each medical management visit. For each of the weekly 10-15 minute follow-up visits, subjects will receive $25. They may earn up to a total of $80 as a bonus for completing all of the daily diaries. Subjects will receive up to $620 for their participation in the study. Medication will be free.

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/aieipa/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.*Cannabidiol has been shown to have a favorable safety profile; it has been well-tolerated in several clinical trials and no adverse events have been reported. Nonetheless, we will monitor safety through the standardized methods described above in the medical management visits. We will have a low threshold for obtaining additional medical workup during the study if the subject reports medical symptoms. If a participant has a clinically significant laboratory or other medical abnormality that cannot be attributed to another cause, the participant's medication will be discontinued and the participant 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 14 weeks. Laboratory data (urinalysis, blood chemistries, complete blood count, electrolytes, and liver function tests) will be done at baseline, 4 weeks, and 14 weeks as well. CBD should not be taken with alcohol, sedatives, hypnotics, or other psychoactive substances because they could potentiate the central nervous system effects of Epidiolex. Thus, 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 the screening visit and monthly during treatment; women who become pregnant will have their medication discontinued and will be referred to an obstetrician; like all participants, they will still be followed for research visits.

Unanticipated problems involving risks to subjects or others, including adverse events, will be reported to the PHRC in accordance with PHRC unanticipated problems reporting guidelines.

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. Epidiolex, while not yet FDA-approved has been well-tolerated in other clinical trials with few side effects. 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.

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.