University of Colorado Boulder

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In addition to the co-investigators listed above, undergraduate and professional research assistants will play an active role in the recruiting and data collection phase of this study. These persons have completed

CITI training, and have been trained by the lead Professional Research Assistant and project manager regarding responsible conduct in research and study specific procedures/guidelines.

I. OBJECTIVES

Please note that the grant proposal supporting this project has now received funding by the National Center for Complementary and Integrative Health (NCCIH). The grant and protocol follow many of the **same procedures as two IRB-approved studies**: "Anxiety, Inflammation, and Cannabis" (protocol number 16-0767); and "An Observational Study of Cannabidiol, Neurocognition, and Mood" (protocol number 14-0087).

The National Center for Health Statistics reports that approximately 76 million Americans suffer from chronic pain, affecting the lives of more Americans than cancer, diabetes, and heart disease combined[1]. Perhaps because of its ubiquity and the challenge to its treatment, relief from chronic pain is by far the most commonly cited condition by patients for use of marijuana, with 87%-94% of medical marijuana users reporting using for relief of a pain condition[2,3]. Although the mechanisms are still unclear, marijuana and its constituent cannabinoids, including 9-delta-tetrahydrocannabinol (THC), are thought to be involved in reducing pain and associated inflammation. However, THC is also associated with harm in the form of cognitive dysfunction. Synergistic interactions of cannabinoids are believed to produce different effects on both pain relief and cognitive function as compared to THC alone. For example, cannabidiol (CBD) is another primary cannabinoid that may work synergistically with THC in a multi-target analgesic approach [a strategy embodied in the pharmaceutical Sativex (aka nabiximols), a CBD/THC based oral spray for pain available in Europe]. CBD does not have psychoactive properties and may modulate the negative cognitive effects of THC. Further, both THC and CBD have anti-inflammatory properties that likely mediate their role in pain relief. However, the anti-inflammatory profiles differ across the two cannabinoids and these differences may impact the mechanistic effects of marijuana on chronic pain. The marijuana products available for pain treatment across dispensaries throughout the US contain a vast array of cannabinoid potencies and ratios. Notably, data from Colorado and other states with legal marijuana suggest that medical users are more likely than recreational users to use edible marijuana, which is a form of marijuana which remains psychoactive much longer than smoked marijuana[4]. The most recent data from Colorado suggest that over 650,000 edible products were sold **per month** in Colorado dispensaries in 2015. Importantly, there have been no reported studies of the mechanistic effects of *edible* marijuana products on pain, inflammatory, and cognitive processes, despite the fact that consumption of edible marijuana is prevalent and rapidly increasing in individuals with chronic pain.

We propose to examine the effects of cannabinoids in edible form on pain relief, inflammation, and cognitive dysfunction in chronic low back pain patients who choose to use marijuana in the context of a short-term (2 weeks) mechanistic study using a patient-oriented, observational design and a Mobile pharmacology and phlebotomy lab that solves many of the logistical problems with marijuana research. **Our global hypothesis is that our observations of self-report and objective measures of the effects of marijuana edible products by pain patients who choose to use these products will vary as a function of the levels of THC to CBD in their blood. Further, we hypothesize that cognitive impacts observed will differ by the THC/CBD levels in blood.** To that end, we will measure the association of pain, inflammation, and cognitive impairment with the levels of THC and CBD in the blood of pain patients who wish to use edible cannabis to treat their pain. This approach is ecologically valid and timely given that edibles of various cannabinoid ratios are widely used by patients in state legalized markets, yet absolutely no research has been done on these products. Edibles generally have either THC-only, CBD-only, or include both THC and CBD. Recent data, including our pilot work, suggest that THC and CBD together produce unique effects on pain, inflammation, and cognition. We will use a patient-oriented, observational design, in which chronic low back pain patients who self-initiate the use of a marijuana edible to manage their pain are observed over their 2-Week study period while using a product of their choosing. THC and CBD blood levels will be tested in relation to all outcomes.

Aim 1. To investigate the mechanisms that may underlie the widespread use of marijuana among pain patients in a 2-week observational study of ad-libitum use, we will observe whether there is an association between cannabinoid levels in blood and measures of self-reported pain.

Hypothesis 1. Based on numerous studies that suggest CBD and THC may work together to produce the analgesic effects of marijuana, we hypothesize that higher blood levels of both THC and CBD will have the strongest association with lower levels of **pain interference** after 2 weeks.

Hypothesis 2. Given the role of elevated **inflammatory markers** as an underlying mechanism involved in chronic pain, we predict that THC and CBD blood levels will additively be most strongly associated with lower levels of four circulating cytokines (TNFα, IL-6, IL-8, IL-1B) after 2 weeks.

Aim 2. To understand the relationship of self-directed edible cannabis-use to cognitive function in individuals with chronic low back pain, we will observe the association between cannabinoid levels in blood and measures of cognitive function.

Hypothesis 3. Based on prior research and our preliminary data, we predict an interactive relationship of blood levels of THC and CBD to cognitive impairment, such that at lower levels of CBD in blood, THC blood levels will be dose-dependently associated with **poorer verbal recall and selective attention** after 2 weeks of *ad libitum* use, whereas at higher levels of CBD in blood, the relationship of THC in blood to cognitive impairment will be attenuated.

II. BACKGROUND AND SIGNIFICANCE

Use of cannabis for chronic pain

The National Center for Health Statistics reports that approximately 76 million Americans suffer from chronic pain; thus, chronic pain (pain lasting more than 12 weeks) affects the lives of more Americans than cancer, diabetes, and heart disease combined[1]. Perhaps because of its ubiquity and the challenge to its treatment, relief from chronic pain is by far the most common condition cited by patients for use of medical marijuana now available in more than half of U.S. states; 87%-94% of self-reported medical marijuana users report using marijuana for relief of a pain condition[2,3]. In addition, there is some evidence that individuals are replacing the use of traditional pain medications with marijuana. For example, one recent study reported survey data suggesting that medical marijuana use in pain patients was associated with a 64% decrease in opiate use[5]. Similarly, recent analyses of prescription data in states with medical access to marijuana suggest a significant reduction in the prescription of traditional pain medications[6]. Finally, a study recently observed significantly lower opiate overdose deaths in states with medical access to marijuana[7]. Combined with the survey data suggesting that pain is one of the primary reasons cited for the use of medical cannabis, these recent reports suggest that a large number of pain patients are replacing the use of opiates with marijuana, despite the fact that cannabis is not an FDA approved medicine for chronic pain. This increased use via medical and recreational marijuana laws suggests there is a strong need for research into the mechanisms that may underlie the effects of marijuana on pain.

Synergistic effects of multiple cannabinoids and pain

Marijuana and its constituent cannabinoids are directly involved in reducing pain and inflammation, including 9-delta-tetrahydrocannabinol (THC) which has well-known analgesic effects. Across five high quality reviews conducted in the past four years, results were largely consistent in suggesting that cannabinoids demonstrate a modest effect on pain[8-12]. For example, a rigorous, systematic review by Whiting et al[11] covered 28 chronic pain studies (2454 participants) primarily conducted in Canada or Europe. Twenty-two of these studies evaluated plant-derived cannabinoids (cannabis extract mouth spray or nabiximols n=13, plant flower that was smoked or vaporized n=5, oral mucosal spray n=3, oral THC n=1) while 5 studies evaluated synthetic THC (i.e., nabilone). All of the selected studies included either an active comparator or placebo control. Analyses across studies that evaluated nabiximols and a single study that evaluated the effects of inhaled cannabis suggested a statistically significant effect of plant-derived cannabinoids on the odds of a 30% or greater improvement in pain (OR=1.41). Nabiximols were

also associated with significant reductions in numerical pain ratings across six additional studies. The largest single effect size presented across the reviews was observed with inhaled cannabis on pain (e.g. OR=3.43[13]). Consistent with this, an average OR of 3.22 (CI: 1.59 to 7.24) was found across 9 doses of inhaled THC tested across 5 studies[8].

While the analgesic properties of THC are the most widely studied, pharmacological and clinical data suggest that cannabidiol (CBD) is another primary cannabinoid that may work synergistically with THC in a multi-target analgesic approach to pain relief. For example, reviews cited above, consistently support that administration of nabiximols, a plant-based mixture of THC and CBD via mouth or nasal spray, provide pain relief. Overall, there is compelling clinical evidence that the synergistic interactions of naturally derived cannabinoids may be effective for pain relief. However, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used cannabis products in the U.S that come in a variety of potencies and cannabinoid contents. Most importantly, it is not clear how the combination of THC and CBD may differ from THC or CBD alone.

Marijuana has anti-inflammatory properties

Cannabinoids have profound effects on immune system function and inflammation, both peripherally and centrally, that indirectly impact their analgesic properties(for review see 14). A number of studies support the notion that the cannabinoids THC and CBD, when considered in isolation, are importation modulators of pro-inflammatory cytokines, including TNF, IL-2, IL-6, IL-12, IL-1β(see 14). Importantly, although both THC and CBD exert inhibitory effects on the production of inflammatory cytokines, their activities seem to involve distinct intracellular pathways which remain somewhat elusive and appear to at least partially involve non-CB1 or CB2 related mechanisms[15]. In addition, pharmacological data suggest that CBD may interact with or alter the effects of THC, suggesting that THC and CBD synergistically may produce different and/or stronger anti-inflammatory effects[16]. Consistent with this, pre-clinical animal studies demonstrate that CBD expands THC's therapeutic window and may enhance the efficacy of THC across a variety of inflammatory conditions, including pain relief [17].

A unique role for THC and CBD in pain through inflammatory pathways

These data, consistent with our pilot data, suggest that THC and CBD have profound anti-inflammatory effects on peripheral and neuro-inflammatory markers(see review 18), which play a pivotal role in pain related therapeutic processes[19,20]. While THC and CBD have anti-inflammatory properties individually, the totality of data, including our own pilot work, suggest that THC and CBD have differing inflammatory profiles[21] which may result in differing effects on pain relief and/or create a synergy whereby a balance of these cannabinoids have the strongest anti-inflammatory and analgesic effects. These exact questions are ideally answered by our proposed design, to examine the range of THC and CBD (both individually and in combination) in edible products chosen by patients. Given that pro-inflammatory shifts are thought to underlie chronic pain, the anti-inflammatory effects of THC and CBD may be key players in explaining associations among marijuana use and relief from chronic pain.

THC and cognitive impairment

In addition to reducing pain and inflammation, studies also indicate that marijuana produces acute cognitive impairment, especially relating to memory and attention during intoxication and possibly for hours to days after use (see reviews 22,23). For example, studies that were published as early as the 1970's suggest that marijuana disrupts immediate and delayed free recall of information(e.g., 24,25). Recall of words from a list is one of the most common approaches to demonstrating the effect of THC on recall performance(e.g., 26). Studies have also suggested that acute marijuana use may interfere with working memory, as evidenced by the effect of marijuana on the digit symbol substitution task (DSST), which some studies suggest may be the working memory measure most sensitive to the acute effects of marijuana(see 27). Among the studies that included two THC concentrations, higher doses mostly yielded greater cognitive impairment[22,28-30]. In neuroimaging work, cannabis users showed differential brain response to an associative memory task while under the influence of THC compared with a placebo. Specifically, THC attenuated brain activity in the insula, right inferior frontal gyrus (IFG) and left middle

occipitals gyrus during encoding, and increased network-wide activity during recall. Taken together, these results suggest that THC has a negative effect on the neurocognitive processes involved with encoding, and neural activation changes during recall likely reflect a compensatory mechanism for the affected encoding. That is, the memory system as a whole must work harder in order to account for the cognitive deficits induced by THC.

In sum, the literature suggests that acute administration of marijuana impairs the encoding and retrieval of information, albeit to a modest degree, and these effects may be dose-dependent on THC level. Further, this cannabis-induced cognitive impairment can last from hours to days after use[22] and potentially longer in heavy chronic users. Thus, the potential cognitive side effects of regular use of current medical marijuana products are highly relevant to pain patients, who may use marijuana on a regular basis to treat their pain and still wish to function well in their daily lives.

Does CBD mitigate the harmful cognitive effects of THC?

Clearly, the evidence suggests that acute marijuana use is associated with at least modest cognitive impairment. However, almost all of this research was conducted with low potency marijuana provided by the government and almost all of this research was focused on the effect of one particular cannabinoid, namely THC. The effects of other primary cannabinoids, such as CBD, are important to consider when interpreting the harmful effects of marijuana use, especially given that marijuana includes more than 80 additional phytocannabinoids[31,32]. Strains commonly available in states like Colorado differ dramatically on the potency of these cannabinoids. As a concrete example regarding the importance of cannabinoids other than THC, several studies have demonstrated that THC and CBD have very different effects on cognition. As noted previously, results from both imaging and non-imaging studies suggest that THC is associated with memory and other cognitive impairment[(see review 22)]. Conversely, analyses suggest that CBD may attenuate the negative effects of THC on cognition and other measures[33-42]. Most of the work on CBD has involved the administration of THC and CBD in synthetic pill form. Much less is known about the combined effects of THC and CBD when using marijuana in the forms commonly available in dispensaries across the U.S. Given that CBD mitigates some effects of THC, this is a high priority area of research in terms of understanding how to reduce the potentially harmful effects of marijuana use in chronic pain patients.

Limitations of existing literature

The majority of studies on cannabinoids and pain[11] evaluated nabiximols (cannabis based oral spray) outside the U.S. Only a handful of studies have evaluated the use of cannabis in the U.S. and all of them evaluated cannabis in flower form provided by NIDA that was either vaporized or smoked. In contrast, most of the cannabis products that are sold in state regulated markets bear little resemblance to the products that are available for research from NIDA at the federal level in the U.S. For example, in Colorado alone >600,000 edible units of cannabis were sold across medical and recreational dispensaries each month of 2015, nearly a 50% increase from the monthly data reported for 2014, the first year of legal marijuana sales in our state[43]. Data also suggest that pain patients are more likely to use edible products than recreational users [43]. Importantly, using marijuana in edible form represents a very different way to use marijuana, in part because in contrast to *smoked* forms of marijuana which produce acute effects that begin to diminish rapidly after consumption (blood levels dramatically decrease within 15 minutes of smoking), *edible* marijuana produces prolonged effects that last at least 4 hours post-consumption[44,45]. This in part explains their increased use in pain patients who seek sustained relief. However, no data are available to understand the mechanisms or effects of edibles of various potencies and cannabinoid ratios. Thus, while the use of particular forms of cannabis for the treatment of pain is supported by well-controlled clinical trials as reviewed above, very little is known about the efficacy, dose, routes of administration, or side effects of *commonly available and increasingly used edible cannabis products*. **More research is desperately needed on the various forms, routes of administration, and combination of cannabinoids, given the ubiquitous availability of cannabis products in much of the nation and the complete lack of any research in the U.S. on the beneficial or harmful effects of edible marijuana.**

III. PRELIMINARY STUDIES

Prior experience and expertise of the team

The PI (Bidwell) takes a transdisciplinary approach to the risks and determinants of marijuana and other substance use. She and her team have conducted complicated randomized controlled intervention trials with laboratory assessments and longitudinal follow-up. The PI and Co-Is Bryan and Hutchison have extensive experience in the integration of neurocognitive and biological assessments into longitudinal behavioral research (e.g. R01 DA025074, PI Hutchison; site PI Bidwell; Co-I Bryan; R01AA024632: PI Hutchison; Co-I's Bidwell and Bryan; R01DA039707: PI Hutchison; Co-I's Bidwell and Bryan), and Co-I Hutchison is also an expert on the testing of neurocognitive and inflammation biomarkers.

Previous and Current Marijuana Studies

Our lab has been conducting behavioral and imaging research on marijuana[46,47] as well as observational research on the relationship of marijuana use to broader health behavior[48-50] for many years. More recently, the lab has focused on the development of cutting edge observational designs to examine the effects of various types of marijuana. One current pilot study utilizes an experimental design compared to the observational one proposed in this application but with many of the same outcome measures. In the pilot study, regular marijuana users (n=22) were asked to switch strains for three days after a washout period. Participants used either +THC/-CBD (~14% THC, <1% CBD) or a +THC/+CBD (7% THC, 14% CBD) *smoked* strain that is acquired from a local dispensary. Both the researchers and participants are blinded to strain condition, and the blind is maintained by the dispensary and one senior member of the lab. After a washout period of no marijuana use, participants use the assigned marijuana strain daily for three days, including the last use on the third day. Blood draws and assessment of cognitive responses are collected before the 3-Day use period at the Baseline Appointment (i.e., after washout), immediately after and 1 after the last self-administration use, at the 3-Day Appointment (participants come to the lab by taxi within 15 minutes of last marijuana use). In our ongoing studies, participants' complete similar measures in our Mobile pharmacology and phlebotomy lab, as well as the currently proposed motor battery.

This pilot work provides proof of concept and hypothesis-consistent data on several levels. 1) It confirms that we can work with our IRB, legal team, and local dispensaries to recruit participants and complete the proposed research. 2) Our pilot data suggest that CBD blood levels are associated with mitigating THC-associated verbal recall deficits. These effects further support our hypothesis that the harmful effects of marijuana vary by THC vs CBD composition across different strains. 3) It shows that we have measured peripheral inflammatory markers (e.g. TNF-a, IL-1B, IL-6) in our participants prior to strain assignment (Before 3-Day Self-Administration), immediately after last use (Immediately After 3-Day Self-Administration), and 2-hours post use (2 Hours After last 3-Day Self-Administration), and that these markers vary based on cannabinoid blood levels. The cytokine associations among marijuana strains are in the hypothesized direction (e.g., use of +THC/+CBD marijuana is associated with the lowest cytokine levels and the strongest anti-inflammatory responses, while the +THC/-CBD strain is associated with comparatively higher levels of inflammation Thus, effects on peripheral inflammatory markers suggest that strains that include both +THC and +CBD may have more positive effects on inflammatory responses than +THC alone. Given the limited scope of the pilot study, we were not able to test the range of edible products (i.e., CBD only) or collect measures of sleep and physical activity (subjective and objective) that potentially mediate inflammatory and cognitive effects, but will in the current proposal.

IV. RESEARCH STUDY DESIGN

Overview and Design of the Proposed Study

A sample of 289 patients who report chronic (at least 12 weeks) low back pain and the intention to try marijuana products for pain relief will be collected. Although the origin of chronic pain is heterogeneous and diagnostically complex, with subjective, affective, and cognitive components, self-report is the backbone of a medical diagnosis[51]. Thus, we rely on self-report of pain intensity and duration for inclusion decisions for our study. Participants need to have at least one instance of lifetime marijuana use, but must have less than weekly marijuana use for the prior six months. Additionally, participants must not have used marijuana at *any time* for the treatment of their pain. As such, participants will be naïve to the use of marijuana for pain, but not to marijuana consumption in general. Recruitment will be via a number of sources that have been used successfully by our research team (described below). If the patient meets minimum eligibility criteria (also described below) and is interested in participating, they will set up an appointment to come to the CU Change Lab for their Baseline Appointment (1st Appointment) involving consent, extensive measures of health behavior (e.g., substance use, sleep quality, physical function, mood, health history, etc.), a blood draw to determine cannabinoid levels and biomarkers of inflammation, and baseline assessments of their low back pain and cognitive function.

During this Baseline Appointment, a research assistant will provide information on three observational, at-home aspects of the study: 1) the range of edible cannabis products, prices, and nearby locations where participants may choose to purchase and 2) the ActiGraph wearable watch device that participants will be loaned to measure physical activity and sleep. Because the study is observational we will not assign individuals to a type of edible product. Instead, we are recruiting individuals who have indicated that they are unsure of what marijuana product to try and therefore want to try different marijuana products. We then inform them about available products and ask that they inform us of their subsequent choice. Participants will then self-administer the product as they see fit, without any instructions from study staff, for 2 weeks. As an exploratory endpoint, we will track participant's self-reported pain level, marijuana use, and sleep pattern with a *daily follow-up message* (online via email) over the course of these 2 weeks. This aspect will provide important data on patient choice, patient behavior, and edible impact on pain.

After the initial 2-Week administration period, patients will be scheduled for their follow up 2-Week Appointment (2nd Appointment) in our mobile pharmacology and phlebotomy lab to examine the acute and mechanistic effects of the product. Following the 2-week edible self-administration period, this 2nd Appointment will involve assessments from Baseline repeated at three time points: once immediately Before, 1 hour after, and 2 hours after the last edible use during the 2-week study period (i.e., Pre-administration, Post 1-hour , & 2-hour administration). The details of each time point are provided below. While the main observational portion of the study will be complete after this 2-Week Appointment, we will continue to track participant's self-reported pain level, sleep pattern, and marijuana use with a *monthly follow-up survey* (online via email, over the course of a six-month follow-up), in keeping with the observational and exploratory nature of the design. This aspect will provide important data on patient choice, patient behavior, and the effects of other marijuana products on pain.

The complete schedule of assessments taken at each Appointment are outlined in Table 1 and described in detail below. Additional details regarding sample ascertainment, marijuana edible selection procedures, power analyses, and the analytic plan follow.

Table 1. Schedule of assessments.

Assessment	Includes	Time to Complete
1. Orientation Assessments: ASAP after screening [Part of Baseline Appointment]	- Description of study procedures and measures - Informed consent; Eligibility re-screening - Edible product selection	~0.5 hour

2. Baseline Assessments: Same day as orientation [Part of Baseline Appointment]	- Pregnancy test, Blood Alcohol Content, Toxicology drug screen - Self-report of pain intensity & interference - Questionnaires on health behavior, substance use, and psychological measures - Inflammation and cannabinoid blood draw - Motor and Cognitive battery - Wearable device distributed	~1.5 hours
3. Daily Follow-up Assessments: 1x/day for 2 weeks of *ad libitum* edible use Between Baseline and 2-Week Appointment	- Daily online message report on pain management, marijuana use (if used: amount, strain, method), and sleep; individually tailored links	~2-5 mins/day
4. 2-Week Mobile Assessments: Before, 1, and 2 hours after self-administration 2-weeks after Baseline Appointment	- All Baseline measures (wearable device collected) - Additional surveys on Impact of Marijuana	~3 hours
5. Monthly Follow-up Assessments: 1x/month for six months After 2-Week Appointment	- Monthly online survey; individually tailored links	~10-15 mins/month
Total time (6.5 months)	**Participants paid $220**	**~6.5 hours**

Marijuana Administration at Home

The proposed work will utilize a design that is observational and does not involve assignment by the research team. More specifically, patients who are already planning to try marijuana as a treatment for their pain will choose their own product at baseline and inform staff of their choice. The patient will then purchase the product at a dispensary. The patient will be observed before they purchase and begin using their product (Baseline Appointment), during use (Daily follow-up messages), and after 2-weeks (2-Week Appointment) of using their product *ad libitum* at home. After the 2-Week Appointment, we will complete Monthly follow-up surveys with the patient for 6 months to determine what additional products the patient may have tried and to collect self-report information on product use and current levels of pain.

Specifically, at the end of the Baseline Appointment, individuals will be asked to select and purchase an edible marijuana product to use *ad libitum* for the next 2 weeks. Colorado requires all edibles to be tested by a state lab, which allows us to have a precise measure of potency after the participants purchase their products. Importantly, the researchers who conduct the assessments as well as all the senior investigators *will* be blind to the participant's product choice. Participants will use their selected product at home consistent with the packaging directions, direction from their physician, or as they see fit, and will be asked not to use any other marijuana product during the 14 days before their 2-Week Appointment (with one Pre- and two Post-administration mobile assessments on the final day of the 2-week ad libitum study period). **Study staff will not provide any directions regarding dosing and administration.**

Rationale for Marijuana Administration Procedure

With respect to the naturalistic aspects of the design, it is important to note that we carefully considered alternative designs. The federally sourced marijuana supplied through NIDA does not currently offer any edible marijuana products (www.drugabuse.gov), although these are widely available through Colorado dispensaries and used in great numbers by Colorado residents and patients to provide relief from chronic pain. Thus, we are not able to acquire marijuana edibles via NIDA-supply and administer them directly to participants via a tightly controlled randomized clinical trial. Given the dearth of data available on why so many people are turning to marijuana as a treatment for pain and on the effects of marijuana edibles more broadly, we developed our design that naturalistically reflects common routes and methods of administration of marijuana in medical patients, particularly in states with legalized marijuana. Because the long-term goal of this work is to better understand the effect of different levels of

cannabinoids in edible marijuana in pain patients, as they are used real world, we decided that it was critically important to emphasize external validity. The disadvantage of our observational design is that we do not have direct control over the choice of product or the dosing and administration of the marijuana. To address this limitation, both in our pilot study and in this application, we rely on blood quantitation of cannabinoids to determine the level of THC and CBD in each subject. Thus, regardless of which product the participant uses or how much of the edible is consumed, we have an objective measure of circulating THC and CBD for each subject, which is the sine qua non of pharmacological research. This aspect is also critical for our analytic approach, which is the analysis of THC and CBD levels in blood.

Finally, it is worth noting that being a major research university in a community that was the first in the United States to legalize recreational marijuana use gives us the unprecedented opportunity to be at the forefront of innovative research to build the knowledge base on marijuana harm reduction. As such, we have worked very closely with the legal team at the University of Colorado to develop our methodological approach so that it does not violate any federal laws, such as the Controlled Substances Act and Drug Free Schools Act.

Blood Analyses of Inflammation

As noted in the background and in our description of our preliminary studies, we expect that CBD and THC will reduce biomarkers related to inflammation during the course of the study. Blood samples drawn at each assessment will be assayed for IFNg, IL-1a, IL-1b, IL-6, IL-2, IL-4, IL-8, IL-10, IL-12, and TNF. Previous studies in animals [52] and humans[53], as well as our own preliminary data, suggest that cytokine activation is associated with the pathophysiology of pain. This is the same assay used in our preliminary studies. To that end, 40 mL of whole blood will be drawn at each assessment point. We will collect 40 ml of blood at each blood draw. We will use 24 ml of blood to perform the inflammatory analysis, and 16 ml of blood for cannabinoid analysis. There will be four blood draws total, with one during the 1st Appointment (Baseline) and three (each separated by an hour) during the 2nd Appointment (2-Week Mobile Van). We will measure changes in cannabinoid and inflammatory levels after the long (2-week pre) and short/acute (1 and 2hour post) time course of edible consumption.

Power Analysis and Sample Size Requirements

Sample size was selected to permit analysis of the primary research questions at two-tailed alpha of .05 and power level of .80. Estimates of effect size follow Cohen[54] and were conducted in G*Power 3[55]. We will rely on cannabinoid blood levels (e.g. THC and CBD and their relevant metabolites) as continuous independent variables to predict study outcomes. Thus, we will be testing regression coefficients in the context of a multivariate model with, in the simplest case, three predictors (THC level, CBD level, and the THCXCBD interaction). With a sample of 246 participants, we will be able to detect effects as small as $f^2 = .04$ with power = .88. This is critical particularly for hypotheses as in each case we predict interaction effects of THD and CBD in blood. It is well known that tests of interactions in non-experimental, observational designs are notoriously small[56], and thus it is critical that we are adequately powered to detect small effects.

The impact of attrition

It is anticipated that some attrition will occur. Based on our current pilot study and previous marijuana studies, we anticipate a 10-15% attrition rate between the Baseline and the 2-Week Appointment. Though we have not experienced differential attrition by condition, and do not anticipate attrition by edible selection, we assume an approximate 85% retention rate over the course of the primary data collection. To adjust for this attrition rate, we will recruit n≈289 participants.

Statistical Analysis Plan

Analyses will be conducted primarily on the SAS system for Windows Version 9.4[57] which includes capabilities to test multilevel models that appropriately model both normally and non-normally distributed data as well as missing data. The distributional properties of continuously scaled variables

will be examined for skewness and kurtosis to determine appropriate analytic techniques or normalizing transformations prior to the primary analyses.

Specific Aim 1:

Hypothesis 1

Objective 1: We will observe levels of pain in individuals with chronic low back pain who engage in 2 weeks of *ad libitum* use of marijuana edible product of their choice with various cannabinoid content. *Hypothesis 1* predicts that observed THC and CBD blood levels will impact lower levels of low back pain interference after 2 weeks, compared to THC or CBD blood levels considered in isolation.

Primary endpoint/analysis: The Roland Morris Disability Questionnaire (RMDQ[58,59]) has been used in studies of low back pain and asks participants about how their experience of low back pain interfered with 24 daily activities in the past two weeks; total score ranges from 0-24. Using the total RMDQ score, we will test pain interference using two time points – Baseline (prior to taking any cannabis) and 2-Week Pre-administration (after 2 weeks of product use but immediately before last edible use in the 2-Week study period). We will test a ordinary least squares (OLS) regression model in which blood levels of CBD, THC, and the CBDxTHC interaction are used to predict 2-Week pre-administration pain interference controlling for Baseline pain interference. Note that our participants are naïve to recent cannabis use at Baseline (per our eligibility criteria) so it is not necessary to control for Baseline levels of cannabinoids. Thus we are testing the effect of blood levels of cannabinoids on experience of recent pain interference. We predict that higher levels of THC and CBD will be associated with less pain interference.

Secondary endpoint/analysis: Using the "current pain" version of the Pain Intensity scale (i.e., "Rate your pain level right now." on a scale from 0-10) we will test acute effects of cannabinoids on pain at the 2-Week Appointment, using three time points: a) Pre administration (before the last edible use), b) Post-1h administration (1 hour after the last edible use), and c) Post 2h administration (2 hours after the last edible use) of the 2-week *ad libitum* study period. We will test a RCR model in which changes in blood levels of CBD, THC, the CBD x THC interaction time (pre administration, 1-hour post-administration, and 2 hours post administration) and all possible interactions are used to predict pain. All independent variables in this analysis are within-subjects as they occur over time. Thus, we are testing the effect of changes in blood levels of cannabinoids on changes in acute pain. We predict that greater increases in THC and CBD acutely will be associated with greater decreases in pain, and that there will be interactive effects such that those participants with the greatest increases in both THC and CBD will experience the greatest decreases in acute pain.

Other secondary endpoints will be analyzed using the same modeling structure described above as appropriate and include: Pre-administration Pain intensity over the two weeks prior to the 2-Week Appointment (average of current, worst, and average back pain over the prior two weeks); Pre-administration Depression, Anxiety, and Stress subscales of the Depression Anxiety Stress Scale (DASS[60]) over the prior two weeks; the Patient Global Impression of Change scale[61] which asks participants to rate their improvement in pain over the prior two weeks on a 7-point scale (completely gone, much better, somewhat better, a little better, about the same, a little worse, and much worse).

Hypothesis 2

Objective 2: To observe levels of circulating cytokines in individuals with chronic low back pain who engage in 2 weeks of *ad libitum* use of marijuana edibles with various cannabinoid content. *Hypothesis 2* predicts that THC and CBD blood levels will additively impact lower levels of circulating cytokines after 2 weeks and after a single use compared to THC or CBD blood levels considered in isolation.

Primary endpoint/analysis: Using the levels of four *individual* circulating cytokines (TNFα, IL-6, IL-8, IL-1B) after two weeks, we will test level of recent inflammation using two time points: a) Baseline

(prior to taking any cannabis) and b) Pre-administration (after two weeks of product use but immediately before the last edible use in the 2-Week study period). We will test an OLS regression model model in which blood levels of CBD, THC, and the CBDxTHC interaction are used to predict pre-administration inflammation controlling for baseline inflammation. Note that our participants are naïve to recent cannabis use at baseline (per our eligibility criteria) so it is not necessary to control for baseline levels of cannabinoids. Thus we are testing the effect of blood levels of cannabinoids on recent inflammation. We predict that higher levels of THC and CBD will be associated with lower levels of inflammation, and that there will be interactive effects such that those participants with the highest levels of both THC and CBD will experience the lowest levels of inflammation.

Secondary analysis/endpoint: Average Z-scored value for the panel of circulating inflammatory markers (IFNg, IL-1a, IL-1b, IL-6, IL-2, IL-4, IL-8, IL-10, IL-12, and TNFα). Using the average of our panel of inflammatory markers, we will test level of recent inflammation using two time points: a) Baseline (prior to taking any cannabis) and b) Pre-administration (after two weeks of product use but immediately before final edible use in the 2-Week study period). We will test an OLS regression model in which blood levels of CBD, THC, and the CBDxTHC interaction are used to predict pre-administration inflammation controlling for baseline inflammation. Note that our participants are naïve to recent cannabis use at baseline (per our eligibility criteria) so it is not necessary to control for baseline levels of cannabinoids. Thus we are testing the effect of blood levels of cannabinoids on recent inflammation. We predict that higher levels of THC and CBD will be associated with lower levels of inflammation, and that there will be interactive effects such that those participants with the highest levels of both THC and CBD will experience the lowest levels of inflammation.

Specific Aim 2:

Hypothesis 3

Objective 3: To observe cognitive function in individuals with chronic low back pain who engage in 2 weeks of *ad libitum* use of marijuana edibles with various cannabinoid content. *Hypothesis 3* predicts that THC blood levels will dose-dependently impact poorer verbal recall and selective attention after 2 weeks, whereas the CBD bloods will attenuate cognitive impairment.

Primary endpoint/analysis: Age and sex-corrected scores from the Flanker Inhibitory Control and Attention task (FICA) and the NIH toolbox cognitive battery and delayed Verbal Recall Memory from the International Shopping List Task are our co-primary outcomes. We will test level of recent cognitive impairment using two time points – Baseline (prior to taking any cannabis) and Pre-administration (after 2 Weeks of product use but immediately before the last edible use in the 2-Week study period). We will test an OLS regression model model in which blood levels of CBD, THC, and the CBDxTHC interaction are used to predict Pre-administration cognitive impairment controlling for Baseline cognitive impairment. Note that our participants are naïve to recent cannabis use at Baseline (per our eligibility criteria) so it is not necessary to control for Baseline levels of cannabinoids. Thus we are testing the effect of blood levels of cannabinoids on recent cognitive impairment. We predict that higher levels of THC and lower levels of CBD will be associated with higher levels of cognitive impairment, and that there will be interactive effects such that those participants with the highest levels of THC and the lowest levels of CBD will experience the highest levels of cognitive impairment.

Secondary analysis/endpoint: Using our co-primary measures of cognitive impairment listed above, we will test acute effects of cannabinoids on cognitive impairment at the 2-Week Appointment, using three time points: a) Pre administration (before the last edible use), b) Post-1h administration (1 hour after the last edible use), and c) Post 2h administration (2 hours after the last edible use) of the 2-week *ad libitum* study period. We will test an OLS regression model in which changes in blood levels of CBD, THC, the CBDxTHC interaction, time (pre-administration, 1hour post administration and 2 hours post administration) and all possible interactions are used to predict acute changes in cognitive impairment. All independent variables in this analysis are within-subjects as they occur over time. Thus we are testing

the effect of changes in blood levels of cannabinoids on changes in acute cognitive impairment. We predict that greater increases in THC and smaller increases in CBD acutely will be associated with greater increases in cognitive impairment, and that there will be interactive effects such that those participants with the greatest increases in THC and the smallest increases in CBD will experience the greatest increases in acute cognitive impairment.

Another secondary endpoint includes the total score from the self-reported subjective cognitive functioning from the Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog[62]) scale, which assesses perceived cognitive impairments, abilities, and quality of life.

Exploratory Analysis (Specific Aims 1 & 2):

Daily: Follow-up online message data on marijuana use and pain during 2-week period of *ad libitum* use

Multilevel modelling via random coefficient regression (PROC MIXED or PROC GLIMMIX in SAS Version 9.4) will be used to test between and within-participant relationships between marijuana use and pain in daily message data[63]. Conditional models will be specified with random and fixed effects of marijuana use (modelled as either yes/no for daily use or as quantity of use) predicting pain intensity or pain interference. To account for repeated measures over time, an autoregressive covariance structure will be used for all models. For the continuous quantity of use measure, following Wang and Maxwell[64], between- and within-participant effects will be disaggregated by person mean-centering the marijuana quantity variable (subtracting the average quantity of marijuana use for that individual), and including time (in days since baseline) as a covariate to detrend the outcome variable (pain intensity/pain interference) in case there are any linear trends in pain over time. The test of the fixed effect of the person mean-centered marijuana quantity variable indicates whether on average there is a significant within-participant relationship between marijuana quantity of use and pain. The test of the fixed effect of the person-mean marijuana quantity (each individual's own average marijuana quantity) indicates whether there is a between-participant relationship of marijuana quantity of use to pain intensity/interference. Due to the intensive longitudinal nature of the design, we will have more than enough power with n=246 participants to estimate these models. In addition, the random coefficient regression procedures allow us the capability of using modern approaches to the handling of missing data[65] including full information maximum likelihood estimation.

Monthly: Follow-up online survey data on marijuana use and pain after 2-week period of *ad libitum* use

The prospective data we are collecting on a monthly basis for six months after the 2-week ad libitum phase allows for the possibility of changes in marijuana use over time and tests of the extent to which those changes vary with changes in pain intensity or pain interference. We do not have *a priori* hypotheses about what will occur during this six-month time frame so these analyses are exploratory in nature. In order to explore these data, we envision that the primary version of this analysis would be parallel process latent growth modeling (LGM)[66]. With this analytic strategy we can statistically test whether the change in frequency or quantity of marijuana use (slope) over time is positive or negative, whether the change in pain is positive or negative, and whether there is an association between the slope in change of marijuana use and pain over time. Importantly, should edible groups arise in our data, it is also possible to conduct a cross-groups parallel process LGM in which the model is simultaneously estimated and the moderation of each path in the model can be examined to determine whether it differs in the groups. For example, we could stratify the analyses by type of marijuana product chosen by the participant (high THC versus low THC), and then test the model of marijuana use and pain as a cross-groups model by marijuana use characteristics. These analyses, while exploratory, will provide important naturalistic data on marijuana use among chronic pain patients over time, and lay critical groundwork for future studies in this area. We have estimated similar models with ~200 participants[67], so we anticipate adequate power for these exploratory models in the current study. Further, LGM incorporates full

information maximum likelihood of missing data, which allows us to maximize the sample size[65]. Because these analyses are exploratory, we will also examine graphical presentations of growth curves in addition to traditional null hypothesis significance tests.

Interim Analyses

We do not plan to analyze any primary or secondary *outcome data* prior to reaching a sufficiently powered sample. We will examine descriptive data as appropriate throughout the study, e.g. to determine whether recruitment efforts need to target particular groups to increase diversity. But we will not conduct tests of any of our hypothesized primary endpoints until the dataset is locked.

V. FUNDING

This study is funded by a grant from the National Center for Complementary and Integrative Health (NCCIH).

VI. ABOUT THE SUBJECTS

Ethnic diversity of this sample is expected to be representative of the greater Boulder-Denver area at large, such that approximately 20-30% of the final sample will represent Latino and non-Caucasian individuals. A trained research assistant will screen prospective participants who call, email, or complete an online survey, according to the inclusion/exclusion criteria below (Table 2). In order to increase consistency between our observational study and published clinical trials in low back pain patients[68], we will recruit individuals between 21 to 70 years of age with non-specific low back pain that has persisted at least 3 months. Given potential confounding influences on inflammatory markers (e.g., IL6, TNFa) and pain outcomes, we will exclude indviduals who report daily tobacco use, an immune-related disease (e.g., HIV), use of antivirals, steriods, psychotropic medications other than anti-depressant SSRIs and ADHD stimulant and non-stimulant medications, or maximal doses of NSAIDs. Use of opiates, anti-depressants, ADHD medications, menstrual cycles, and birth control will be tracked during the study. Specific criteria for study participants are listed in Table 2 below.

Table 2. Inclusion/Exclusion criteria.

Inclusion	Exclusion
Self-reported low back pain ≥ 3 months	Low back pain with pain intensity rated at less than 4 and pain interference with activities rated at less than 3 (on 1-5-point scales)
At least one episode of lifetime marijuana use, but less than or equal to weekly marijuana use for prior six months	More than weekly use of marijuana in prior six months, or use of marijuana to treat their low back pain *at any time* in their lives
Intent to initiate use of marijuana to treat their low back pain	Actively seeking or in treatment for any substance use disorder; Report of drug use in past 72 hours before Baseline

	Appointment (other than opiates) or failed urine screen (e.g., cocaine, methamphetamine, etc.).
21-70 years of age	Daily tobacco use (cigarette, E-cigs, and smokeless)
Able to provide informed consent Health eligibility approved by study physician when applicable	Current diagnosis of bipolar disorder or schziophrenia, use of psychotropic medications (other than SSRIs and ADHD meds), antivirals, steriods, or maximal doses of NSAIDs
	Acute illness other than low back pain or any immune-related disease (e.g., HIV; See excluded illness list below.)
	Females cannot be pregnant, or trying to become pregnant

Self-reported information that determines eligibility will be exclusionary at Screening (online or on the phone) only (e.g., concomitant medications), not throughout study.

Ineligible if any of these illnesses are present currently or occurred in the last month: Hemophilia, HIV, Concussion (Grade 3 – Loss of Consciousness), Pulmonary Embolism, Stroke, Myocardial infraction, Liver Disease (Cirrhosis or hepatitis), Leukemia or Lymphoma, Ablation Therapy for Arrhythmias or any treatment for heart Arrhythmias, Heart Murmurs or Heart Disease, Tuberculosis, Trauma with Internal bleeding (i.e. Abdominal Aortic Aneurysm)

VII. VULNERABLE POPULATIONS

This study does not include any vulnerable populations.

VIII. RECRUITMENT METHODS

Recruitment will be via a number of sources that have been used successfully by our research team. First, as in our pilot project, we will recruit using flyers posted in and ads on the webpages and social media pages of dispensaries in the Denver and Boulder areas. Second, with assistance from Dr. Rzasa-Lynn, as well as local health care providers and physicians, we will advertise our study with flyers (see attached flyer) in and referrals from local pain clinics. Third, we will utilize targeted mailings, advertising the opportunity to participate in our observational study. We will obtain a list of names and addresses of individuals who fit our target demographics and geographical area. These names/addresses are obtained from publicly available records purchased from a marketing firm (see http://www.alescodata.com/reseller-programs.html). Recruitment materials are mailed to each address on the list. We can narrow the list based on age, gender, geographic location, and other criteria. Fourth, we will use the NIH-funded free ResearchMatch (see https://www.researchmatch.org/) tool to link health criteria from potential participants to our specific research criteria. ResearchMatch has a large population of volunteers who have consented to be contacted by researchers about health studies for which they may be eligible. In addition to ResearchMatch, we will be utilizing the free online clinical trial matching platform HealthMatch (see https://healthmatch.io). HealthMatch is a resource for persons interested in clinical trials. It is similar to ResearchMatch and also has a large population of volunteers who consent to be matched to health studies for which they may be eligible. We will also advertise on free platforms like online patient groups and pay for platforms (e.g. Facebook/Twitter advertising) that often allows for targeting advertisements based on age, geographic location, and interests (e.g., following or "liking" posts related to chronic pain).

In summary, we will recruit subject locally and primarily through: target ads on pain groups in Facebook, mailing flyers w/purchased names & addresses from Alesco and NIH-based ResearchMatch

tool, flyers and referrals from doctors' offices (Orthopedic, Chiropractic, Rheumatologist, Physical Therapists, Occupational Therapists, Pain Specialists, etc.), recreational and alternative health centers (e.g., yoga studios, acupuncture and massage specialists, and gymnasiums, etc.), as well as in local restaurants and shops in Boulder. The combination of these varied recruitment methods should provide ample and steady potential participants, as in previous studies similar in size. All interested participants will be directed to complete an online screening survey (via RedCap) or to contact the CU Change Lab by phone or email (to be screened over the phone).

IX. COMPENSATION

Participants will receive $220 for completing all aspects of the study: $60 in cash and for the Baseline Appointment (1st in-person Appointment) and $100 for the 2-Week Appointment (2nd in-person appointment). Participants will receive $1/day for each of the daily follow-up messages that they complete during the two *ad libitum* period, with a possible bonus of $6 for completing at least 12 of the 14 daily messages, for a maximum of $20 extra paid in cash at the 2-Week Appointment ($120 total). Participants will receive a $5 Amazon.com gift card for each of the 6 brief Monthly follow-up surveys completed, plus a bonus $10 Amazon.com gift card for the final assessment ($40 total, delivered online via email). If a participant does not complete the study, payment will be pro-rated for the Appointments/online follow-up assessments that they do complete, in person, and in cash. Given the amount of time required in the study and the travel to and from the lab for the 1st Appointment, this is a reasonable amount of money to compensate participants for their time and effort. Thus, there is no question of coercion.

X. CONSENT PROCESS

When a participant arrives for their 1st Appointment at the Center for Innovation and Creativity (CINC), a member of the research team will greet them in the 1st -floor lobby. The research assistant will take the participant to a private room and provide the participant with a copy of the informed consent document. Prior to asking the participant to sign the consent form, the trained research assistant and the participant will have a discussion regarding the research study. Additionally, the research assistant will be available to answer any questions they may have about the study. We will also explain that participation includes a study appointment in our Mobile Van Pharmacology and Phlebotomy Laboratory, which will be seen outside their home, possibly by their neighbors, and that privacy may not be maintained. Participation will be clearly stated as **voluntary**, with the option to withdraw at any time. There will be **no deception** involved with this study. After discussing the study and all measures, and going over the consent form with the researcher, the participant will be included in the study if they choose to initial and sign the informed consent document.

XI. PROCESS TO DOCUMENT CONSENT IN WRITING

In accordance with 45 CFR 46.117, a printed copy of the written informed consent document will be signed by the participant after all of his/her questions have been answered and prior to the start of any experimental procedure. Additionally, an unsigned copy of the form used to document consent will also be given to the study participant electronically.

XII. PROCEDURES

Participants will contact the researchers with their interest by phone, e-mail, or through an online screening survey (RedCap, provided as a CCTSI resource). In the case that a potential participant requests more information via e-mail or voicemail message, the research assistant responding to the message will ask the participant to call the lab phone number for more information (same phone number provided on all study advertisements), e-mail the study team a phone number at which the potential participant could be reached at and a desirable time for the research staff to call, or to complete the online survey. The first page of the online screening survey will give a brief description and the estimated time involved in completing the screening process and the observational study (in the case that they are eligible and elect to participate) and instructed to click the *Next Page* button if they wish to be screened further. The online screening that follows will be identical to the phone screening. All subjects that complete the screening will be asked to leave their preferred contact information and the best time to contact them so that a research assistant can inform them of eligibility (according to the inclusion/exclusion criteria in Table 2 above) and answer any questions they may have. For participants that prefer to complete a phone screening, a trained research assistant will provide an overview of the study, answer any questions that the potential participant has, and then screen them for preliminary eligibility according to the inclusion/exclusion criteria in Table 2 above. This process will help to ensure participants have ample opportunity to be informed of the main study components and maintain their privacy as much as possible. If the participant meets the study criteria after the initial online screening survey or phone interview and the follow-up contact, they will be invited to come to the CU Change Laboratory at the CINC for their Baseline Appointment. If any subject is questionable for inclusion, our PI and study physician team (Dr. Bidwell, a licensed clinical psychologist and Dr. Rzasa-Lynn, a licensed M.D.) will make the final determination of eligibility.

COVID-19: Before interacting with research assistants, eligible participants will be asked additional questions related to COVID-19. These questions will be administered prior to any in-person appointment and by a research assistant over the phone (or at a distance of at least 6-feet if the participant is unable to complete the questions over the phone). These questions will be administered to protect staff and participants from the spread of COVID-19. The questions are a precaution based on current university and Centers for Disease Control and Prevention guidelines and may need to be updated as the understanding of COVID-19 evolves. These procedural questions are temporary in nature and will be lifted once university guidelines deem it unnecessary.

Baseline Appointment Procedure and Assessments

Subjects who meet inclusion criteria (see Table 2 above) will be scheduled for a Baseline Appointment and given instructions, including not consuming alcohol for 24 hours, tobbacco, caffeine, and any other drugs for 72 hours (excluding those needed for regular pain management) prior to the appointment. Subjects will be reminded to eat a small meal and hydrate well before the baseline appointment. After arriving at the CUChange Laboratory, each subject will go through the consent process and after all questions have been answered and if participants consent, Baseline procedures will begin (see Table 3). A urine toxicology and a pregancy test (for females) will also be administered to verify if subjects have recently taken illicit drugs and to ensure that they are not pregnant. A blood draw will be taken to quantify current use of cannabinoids and inflammatory markers (1st of 4 total blood draws completed during the entire study). All blood draw procedures performed during this study will involve collecting venous blood (40 mL per draw) with venipuncture of a peripheral arm vein using standard, sterile phlebotomy techniques. Subjects will then complete current and historical health and substance use assessments (see section below and Table 3 for details), and a motor and cognitive testing battery.

At the end of the Baseline Appointment, individuals will be asked to self-select an edible marijuana product based on their preference. Participants will then use their selected product at home, consistent with the packaging directions, direction from their physician, or as they see fit, and will be asked not to use any other marijuana product during the 2-Week study period, before their 2-Week Appointment

(Mobile Laboratory assessment). Study staff will not provide any directions regarding dosing and self-administration. While participants themselves will not be blind to their product choice, importantly, the researchers who conduct the assessments as well as most of the senior investigators will be blind to their selection. At the Baseline Appointment, participants will be given instructions and allowed to practice responding to an online daily message prompt (described below), that will commence after they purchase an edible of choice.

Participants will be given an ActiGraph wearable device (described below) to track their physical activity and sleep during the 2-Week observational period (http://actigraphcorp.com/). They will be instructed on how to wear and use the device at this Baseline Appointment. Participants will be instructed to wear the device as long as they feel comfortable during the 2-Week period and to return the device at the 2-Week Mobile Appointment (2nd Appointment). The importance of returning the device will be emphasized to participants and we expect the vast majority of Actigraph watches to be returned at the 2-week Mobile lab Appointment, which takes place at the participant's home. In our prior studies that involved "take-home" devices, such as heart monitors, we had a 96% return rate. For any wearable watch device that is not recovered (for any reason), up to three attempts will be made to contact the participant and collect any wearable watch device that is not recovered (for any reason). The research staff will not make further attempts to collect the device, and will consider the device forfeited and irretrievable after this point. Details on the exploratory Actigraphy data analysis will be provided in a separate Actigraphy Data Analysis Plan.

Research study staff will debrief participants and compensate them with $60 in cash for their time and effort during the Baseline Appointment.

Daily (Online-based) Follow-up Assessments

Assessment of marijuana use (online) has been shown to be feasible in a variety of studies[69,70]. Subjects will answer online survey assessments via email with individually tailored links hosted by our university's licensed survey tool RedCap. During the 2-Week study period, participants will report *daily* on the Pain Intensity item from the NIH Toolbox, their edible marijuana use, other pain management strategies, and their sleep pattern. This brief message report will provide a daily repeated measure of our primary constructs (pain and marijuana use) and potential mediators or moderators over the course of the 2-Week study. All subjects will be given extensive instructions on completing the daily message at the Baseline Appointment and will practice answering the questions in the lab using their cell phone or a lab computer to ensure they understand the process and time commitment. To enhance the response rate, participation on daily follow-ups will be monitored and participants will be contacted if they do not respond for two consecutive days of daily messages. Participants will then be compensated for their time and effort during the 2-Week Appointment, receiving a $1/day with a $6 bonus for completing 12 or 14 online follow up message reports ($20 in total possible).

2-Week Mobile Appointment Procedure and Assessments *(Pre, Post 1hr, & Post 2hr time points)*

Because we wish to obtain our data while the participant is under the influence of their cannabis product, and because it is not safe to operative a vehicle while under the influence, we will bring our state-of-the-art Mobile Van pharmacology and phlebotomy laboratory to the patient's location to complete all 2-Week Appointment procedures (see Table 3). Prior to taking their last edible of the 2-Week study period, participants will come out to the Mobile laboratory to complete their 2nd blood draw, heart rate, motor and cognitive battery and self-report assessments (including quantity of marijuana use and pain severity over the study period). The blood draw will be a venipuncture of a peripheral arm vein using standard, sterile phlebotomy techniques, and 40 mL of blood will be collected. Participants will then return to their home to take their edible.

After taking their edible product, they will return to the Mobile Laboratory 1 hour later. Because 60 minutes is the average time that CBD and THC levels begin to peak in the blood after oral administration of cannabis extract[44,45], assessment of the acute effects of marijuana (e.g., pain, cognition, and inflammation) will begin at exactly 1-hour post-edible consumption (Post 1-hour self-administration).

After peak, cannabinoid levels steadily decrease over the next 2-3 hours and by 4 hours post-ingestion begin to rapidly drop off in blood[44,45] _ENREF_82. To account for individual differences in metabolism and sensitivity, patients will be assessed again at 2 hours (Post 2-hr self-administration). Each assessment time point [Baseline & 2-Week (Pre, Post 1-hr & 2-hr) self-administrations] will include a 40 mL venous blood draw, heart rate, questionnaires, and motor & cognitive battery. Thus, including the Baseline Appointment, a total of 160 mL of blood (40 ml x 4 time points) will be collected for the entire study. After completing the Post 2-hour consumption assessments, participants will hand in their ActiGraph device, they will be debriefed, and the RA will escort them back to their home. Participants will then be compensated $100 in cash for their time and effort during the 2-Week Appointment.

Monthly (Online-based) Follow-up Assessments

After the 2-Week *ad libitum* period of edible use with detailed online and in-person tracking, participants will be asked to provide monthly follow-up information on their pain and marijuana use. All subjects will be given extensive instructions on completing the daily message report at the Baseline Appointment and will practice answering the questions in the lab using their cell phone or a lab computer to ensure they understand the process and time commitment. They will answer online survey assessments with individually tailored links hosted by our university's licensed survey tool RedCap. To track participant behavior and potential effects (e.g., marijuana use and pain levels) naturalistically, a monthly survey will assess self-reported marijuana use, sleep, pain ratings and management, and cognitive effects over the past month, for the six months. To enhance the response rate, participation on monthly follow-ups will be monitored and participants will be contacted if they if they do not respond to one monthly survey. Participants will receive a $5 gift card by mail for every monthly online follow-up survey that they complete, plus a $10 bonus gift card for the final survey ($40 in total possible).

Please see Table 3 for a detailed description of the procedures and measure by appointment and Table 4 (page 26) for a Schedule of Evaluations.

Table 3. Description of observational procedures by appointment.

Name of Instrument/Procedure	*Data collected*	
Eligibility Screening (ES)	Phone Interview or Online Survey questionnaire used to determine subject eligibility (based on Table 2 inclusion/exclusion criteria).	
Baseline Appointment (only)		
Informed Consent (IC)	In-person discussion and review of consent document detailing all observational measures and any questions.	
Medical History (MH)	General assessment of medical history for any major disease or illness, the neuropathic pain scale, and prescribed medication use.	
Toxicology Drug Screening (TDS)	A urine sample will test for recent substance use (e.g., marijuana, cocaine, benzodiazepines, MDMA, sedatives, or methamphetamine) other than pain medications.	
Pregnancy Screening (PS)	All female participants will take a urine pregnancy test and report their last menstrual cycle and any birth control methods.	
Demographics (D)	Age, sex, marital status, race/ethnicity, education, birth date, and height.	
Alcohol Use History Questionnaire (AUH)	Targets the frequency of lifetime and recent use for alcohol.	
Alcohol Use Disorders Identification Test (AUDIT)	The AUDIT[71,72] _ENREF_82 will be used to examine the extent of co-morbid alcohol use and problems related to alcohol use.	

The Beck Depression Inventory-II (BDI-II)	Consists of 21 scaled statements designed to assess symptoms of depression over the past 2 weeks and will be administered to examine comorbid depression and covary baseline differences if necessary[73].	
The Beck Anxiety Inventory (BAI)	Consists of 21 items, each describing a common symptom of anxiety over the past week and will be administered to examine comorbid anxiety and covary baseline differences if necessary (BAI[74]).	
ADHD Self-Report Scale (ASRS)	ADHD Self-Report Scale[75] _ENREF_87, will be used to assess ADHD symptoms in participants, given the high rates of ADHD among marijuana users. This measure consists of 18 items that correspond to the DSM-V ADHD symptoms and are rated over the past six months on a 1 (never) to 5 (very often) scale.	
Baseline & 2-Week Appointment (Pre-administration only)		
Pain Intensity-7d (PIT7)	Consists of two items asking about the participant's level of pain on average and at its worst in the past 7 days. Participants are asked to rate their pain on a scale from 0 (no pain) to 10 (worst imaginable pain).	
Pain Interference-7d (PIF7)	Participants are asked to rate their pain interference in the last 7 days (1-item, PROMIS) on a scale from 1 (not at all) to 5 (very much), as it refers to the degree to which pain limits or interferes with their physical, mental, and social activities.	
Marijuana Dependence Scale (MDS)	The MDS based on DSM-V criteria that were converted to a self-report measure. Individuals respond 'yes' or 'no' to each dependence item (e.g., "When I smoked marijuana, I often smoked more or for longer periods of time than I intended"). The items are then summed to form the scale. This scale has been previously used in the cannabis literature. The internal consistency of the MDS (based on the DSM IV) was good in our pilot study (α=.73) and even better in previously published reports (α=.85[76]).	
Marijuana Purchase Task (MPT)	The marijuana purchase task (MPT) is a valid measure of the relative economic value of marijuana is needed to characterize individual variation in the drug's reinforcing value. This asks participants to estimate the number of marijuana joints they would purchase at increasing prices and can be used to examine the associations between marijuana use and MPT demand indices.	
***Cannabis Questionnaire/Marijuana Users Health Cohort/ (MUHC)**	This modified version details the primary reasons, frequency, and type of cannabis use patterns in occasional and regular users.	
***Impact of Marijuana on Pain (IMP)**	This modified short self-report questionnaire on the impact of marijuana on pain and health compared to other types of pain management (e.g., drugs, opioids, exercise) and the expected and past risks and benefits (e.g., sleep, mood, anxiety).	
Health Related Quality of Life (HRQL)	This is a Short Form 12 Health Survey, which consists of 12 questions across eight health domains and is sensitive in	

	detecting changes in time (one month) in health-related quality of life.	
***Timeline Follow-Back (TLFB)**	TLFB is used to assess daily substance use (for the 2 weeks prior to the Baseline Appointment, and 2 weeks prior to the Mobile Appointment. Our modified TLFB procedure will estimate both frequency of marijuana use and amount used per day, using visual stimuli as well as the method of administration[77,78].	
Blood Alcohol Content (BAC)	Breathalyzer test for recent alcohol consumption.	
Physiological Weight Scale	A digital scale will be used to collect subject weight at each in-person appointment.	
Stadiometer	A ruler with a sliding horizontal headpiece will be used to collect subject height at the Baseline Appointment.	
Pittsburg Sleep Quality Index (PSQI)	Measurement of the quality and patterns of sleep from poor to good measuring seven domains (e.g., latency, duration, disturbances) over the last 2 weeks.	
***Roland Morris Disability Questionnaire (RMDQ)**	This asks participants about how their experience of low back pain interfered with or affected their enjoyment of various daily activities in the past 2-weeks (modified from today). This 24-item self-report asks participants to mark an item if they experienced each type of pain interference, each mark is scored as 1 point, with a total range from 0-24, higher scores demark higher interference.	
Depression Anxiety Stress Scale (DASS)	The DASS is a 21-item short-form self-report instrument for measuring the three related negative emotional states of depression, anxiety, and tension/stress.	
Self-Rated Diet (SRD)	Assesses self-rated quality of overall diet and amount of fruit and vegetables consumed daily, on average. Includes EATS (10 item questionnaire asking about fruit and vegetable consumption in past two weeks) and FVS (3-item measure asking about the health of their diets and daily fruit/vegetable consumption).	
Current Opioid Misuse Measure (COMM)	Standardized measure of opiate misuse, characterizes opiate users in our sample and allows us to draw comparisons to other research samples using this measure.	
Stanford Leisure-Time Categorical Activity Item (L-Cat)	The L-Cat is a single item measure asking about average level of exercise/activities.	
Perceived Stress Scale (PSS)	The Perceived Stress Scale (PSS) is a self-reported scale asking about feelings and thoughts within the last 2 weeks.	
***Pain Interference-current (PIFc)**	Consists of 1-item asking about the participant's level of pain interference currently (modified from the NIH PROMIS). Participants are asked to rate their pain on a scale from 1 (no pain) to 5 (worst imaginable pain).	
2-Week Appointment (only) (Pre, Post 1- & 2-hr administration)		

The Drug Effects Questionnaire (DEQ)	The Drug Effects Questionnaire (DEQ) is a 5 items visual analog scale used to measure the strength of marijuana as well as the desirable effects[79].	
The Addiction Research Center Inventory (M-Scale)	The Addiction Research Center Inventory[80] (ARCI), including the ARCI—Marijuana (M) scale[81] will be used to measure subjective effects of marijuana in addition to drug-induced euphoria, stimulant-like effects, intellectual efficiency and energy, sedation, dysphoria, and other somatic effects.	
Baseline & 2-Week Appointment (Pre, Post 1- & 2-hr administration)		
Heart Rate (HR)	Heart rate will be collected using a basic fingertip pulse oximeter.	
Blood Pressure (BP)	An automated, small, portable machine will be used to collect blood pressure.	
Venous Blood Draw (BD)	A 21-23g needle and vacutainer will be used to obtain 40 mL of blood through a peripheral arm venipuncture using standard, sterile, phlebotomy techniques.	
Pain Intensity-current (PITc)	Consists of 1-item asking about the participant's level of pain currently. Participants are asked to rate their pain on a scale from 0 (no pain) to 10 (worst imaginable pain).	
Motor/Movement Battery (MB)	Physical function assessment of functional reach, dynamic sway (balance) sit-to-stand and finger tapping. A standard smartphone (iPod Touch) will be attached to participant's hand, arm, leg, or waist with a simple elastic/Velcro strap. An App on the device will record their fine grained movements while they perform slow or fast movements with their hand, arm, or leg. Also, they will be asked to stand as still as possible for 30-60 seconds, with eyes open or closed, while the iPod is attached to their hip, trunk, or leg. They will also be asked to tap the smartphone repeatedly for no more than 60 seconds.	
International Shopping List Test (ISLT)	The International Shopping List Task[82] (ISLT) is a computer software program, consisting of a 12-item shopping list that is read out loud to the participant. The participant is asked to recall as many words as they remember. The list of words is presented again in the same order two additional times to facilitate memorization. After 30 minutes, a delayed recall trial is administered and participants are asked to recall the list again. At each session, participants are read a different shopping list.	
Neurocognitive Toolbox Battery (NCB)	From the NIH toolbox, this cognitive battery will include the Flanker Inhibitory Control and Attention task, the Pattern Comparison Speed Test, the Picture Sequence Memory Test, , and the List Sorting Working Memory Test. The battery covers the domains found to be sensitive to the effects of marijuana[83]	
Marijuana Craving Questionnaire (MCQ)	A Marijuana Craving Questionnaire will be used to assess craving at each time point during the experimental session. The MCQ was adapted from a valid tobacco craving questionnaire[84] and has proven to be useful in cannabis studies	

	[85]. In our pilot study, internal consistency was very high (α= .90).	
Alcohol Craving Questionnaire (ACQ)	Asks participants to rate their desire to consume an alcoholic beverage at the current moment, as a self-rated measure of co-administration potential.	
***Profile of Mood States (POMS)**	The modified Profile of Mood States (POMS) will be used to collect baseline information on mood as well as information on mood changes throughout the study[86-88].	
Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)	A subjective measure of perceived cognitive impairments, ability, as it impacts others, and quality or life.	
Patient Global Impression of Change (PGIC)	The Patient Global Impression of Change (PGIC) scale is a subjective measure consisting of 1 question to ask participants any changes in their overall status of pain in the past two weeks.	
Baseline Appointment (CINC Lab)	Informed consent & study orientation; BAC test; Urine toxicology and Pregnancy test; Heart rate; Pain Intensity & Interference ratings; 1st Blood draw; Questionnaires; Cognitive & Motor Battery; Wearable distributed; Appointment 2 scheduling; Monetary Compensation.	120 minutes
Daily Follow-Up Messages	Respond to brief questions (online) about marijuana use, sleep quality, and pain management once per day for 2 weeks after self-directed edible use. Each survey has a 24 hour window before the link expires.	2-5 mins/day x 14 days (~30 mins total)
2-Week Appointment (Mobile Lab) -Pre-administration	Immediately before edible self-administration; Come out to Mobile laboratory; Heart rate; Pain Intensity & Interference ratings; 2nd Blood draw; Questionnaires; Cognitive & Motor Battery; Return home to self-administer edible.	75 mins
-Post 1-hr administration	1 hour after edible self-administration; Return to Mobile laboratory; Heart rate; Pain Intensity ratings; 3rd Blood draw; Questionnaires; Cognitive & Motor Battery; Return home.	45 mins
-Post 2-hr administration	2 hours after edible self-administration: Return to Mobile laboratory; Heart rate; Pain Intensity ratings; 4th Blood draw; Questionnaires; Cognitive & Motor Battery; Return wearable; Debriefing; Monetary Compensation; Return home.	60 mins
Monthly Follow-up Surveys	Respond to brief questions (online) about marijuana use, sleep quality, and pain management once per month for 6 months, Monetary compensation (each month). Each survey has a 2 week window before link expires.	10-15 mins/month x 6 months (~60 mins total)
TOTAL STUDY DURATION (6.5 months)		**~6.5 hours**

Key: *=use of a modified measure

Protocol Deviations: This study is observational in nature, entails multiple exploratory time points and analysis, and asks for a large amount of self-initiated and voluntary participation for each task, with no

previously defined or investigated expected norms or minimum standards for completion. Therefore, if participants decide to not complete a particular assessment(s) they will not be considered a protocol deviation (i.e., if they elect to not answer or complete parts of the Baseline or 2-Week appointment or any/all of the daily or monthly exploratory surveys). However, we will record and account for any missing data in our data analysis (as noted in Section IV Research Study Design – Statistical Analysis Plan). Importantly, our lab has had little difficulty completing all or nearly all of the proposed assessments in ongoing or previous longitudinal studies, scheduling and maintaining similar appointment criteria (i.e., scheduling follow-up visits within a set time window), and collecting multiple blood samples on different visits or within the same visit.

While we do not anticipate deviations from the above procedures, to increased replicability and efficiency of future studies, we will define and record the following events as they may impact the primary outcomes of the study. Therefore, a protocol deviation will be noted (unless missed due only to participant refusal) if:

1) A 2-Week Mobile Lab appointments is not completed within 2 weeks (14 days) ± 4 days from the Baseline appointment (i.e., 2-Week appointment should be ±4 days from the intended 14-day study period), and/or

2) A blood sample collection is not obtained from the Baseline appointment, and/or 2 or more blood sample collections are not obtained from the 2-Week Mobile Lab appointment.

3) An assessment is not administered to the subject due to unforeseeable events (i.e. REDCap system malfunction).

XIII. SPECIMEN MANAGEMENT

Blood samples collected in the mobile lab will be kept in an insulated biohazard transport bag. All blood samples collected during the study will be stored in locked freezers within the PI's laboratory designed specifically for storing biological specimens. Samples will be coded with a randomly generated participant ID number and all data collected will be stored on a password protected server and separate from the master list linking the ID numbers to participants' contact information, also stored on a password protected server and only accessible by a research team member. At study closure, all links between participant name and number will be destroyed, at which point the blood specimens will be considered de-identified. After all analyses are complete, these specimens will be destroyed.

XIV. DATA MANAGEMENT

Signed consent forms will be stored in a locked filing cabinet in the PI's lab at the CINC. All data from self-report and interview measures will be stored on password protected computers and on the PI's password protected server in the CINC, both of which are only accessible to research staff. All stored data will be recorded from secure survey software. Any identifying information will be destroyed after the last appointment (on-line or in-person), and biological samples will be destroyed after all analyses are complete.

XV. WITHDRAWAL OF PARTICIPANTS

Situations in which the entire study may be terminated early include the following: If the Principal Investigator or other governing official discovers serious concerns about subjects' safety, inadequate performance or rate of enrollment (this includes a missed study appointment); because study objectives have been obtained according to pre-established statistical guidelines; or in the unlikely event that the Principal Investigator retires and no other additional investigators are able to succeed his role within the

research project. Though highly unlikely, the circumstances under which a participant would be withdrawn without his or her consent include: obviously not following instructions or behavior that is verbally or physically abusive towards research staff. Those who experience early withdrawal will receive prorated payment based on the number of appointments that they completed.

XVI. RISKS TO PARTICIPANTS

Risks Pertaining to the Legality of Cannabis

The possession and use of cannabis is legal at the state level, but illegal at the federal level. Any risk associated with this study is not greater than risks experienced by participants when they purchase cannabis outside of the study. We will comply with all NIH guidelines, and a Certificate of Confidentiality will be deemed applicable for our study, decreasing the risk for participants.

Risks Associated with Venipuncture

There is a small risk of local hematoma, infection, and syncope associated with phlebotomy. Any risk associated with undergoing four blood draws for a total of 120 ml over ~ five hours in two separate days will be minimized with certified and experienced venipuncture staff, collecting information on the subjects' last meal and by offering a standard snack before the last blood draw.

Psychological Risks and Discomforts

While participants who use cannabis in the context of the research must already be experienced cannabis users in order to be in the study, it is still possible that some participants might experience some adverse effects from the cannabis such as changes in mood/affect, sleepiness, paranoia, and increased heart rate. There is a slight risk that the ingestion of cannabis may be associated with a psychotic episode.

Participants will be monitored during study period by the PI Dr. Bidwell who is a licensed clinical psychologist (Colorado license #4116) to make sure that there are no clinically significant events that occur during the study period, including careful monitoring of suicidal ideation endorsement on the BDI. Levels of pain will be also monitored by study staff and should clinically severe pain be present (Pain intensity of >=8 or Pain interference of 5), the participants will be contacted by the study physician (Dr..Rzasa-Lynn) and referred to their primary care physician or other appropriate treatment. This practice has been used frequently by the PI in other IRB approved studies and the risks for clinically meaningful increases in pain are not expected to be greater than what would be experienced in daily living. Information regarding pain treatment resources and appropriate referrals will be made to each participant at the end of participation, if requested.

Risks Pertaining to Loss of Confidentiality and Privacy

Confidentiality of participants is a priority for research staff and must be maintained unless the investigator obtains the express permission of the participant to do otherwise. Risks from breach of confidentiality include invasion of privacy, as well as social and economic risks. Economic risks include alterations in relationships with others that are to the disadvantage of the subject, and may involve embarrassment, loss of respect of others, labeling with negative consequences, or diminishing the subject's opportunities and status in relation to others. These risks include payment by subjects for procedures, loss of wages or income, and/or damage to employability or insurability.

Participants will be asked and tested for illegal activities that they may have been involved in (i.e., illicit drug use). Participants will also be warned that there are some things that they might tell us that we CANNOT promise to keep confidential, however all NIH funded research involving human subjects and identifiable data, bio-specimens or genomic data, will be issued a Certificate of Confidentiality for all research that is commenced or ongoing after December 1st 2017. Updates to our associated documents (e.g., consent form, see attached) and IRB approval is underway and will be followed and managed, as directed by NIH. Participants will be informed that we are required to report information like child abuse

or neglect, crimes that they tell us they or others plan to commit, or harm planned against themselves or others.

Unanticipated risks

Any experiment may involve risks that cannot be anticipated. If unanticipated risks occur, the investigators will follow the IRB guidelines for adverse event reporting.

XVII. MANAGEMENT OF RISKS

Risks Pertaining to the Legality of Cannabis

The risk is minimal given the legality of cannabis in Colorado.

Protection against risks associated with Venipuncture

The risks of hematoma and infection are minimized by having trained personnel perform the procedures using sterile techniques. Any additional risks are decreased by using the participants preferred arm for venipuncture (in case prior injury or surgery has decreased function) and by reminding participants to adequately hydrate prior to their appointment. In addition, we provide snacks and complete supervision in a seated and protected position to reduce any risk of dizziness or falling.

Psychological Risks and Discomforts

In the unlikely event that an edible cannabis user has an adverse reaction to the edible cannabis product that they have chosen to use at the mobile clinic visit and needs assistance, the research assistant will immediately notify Dr. Bidwell who will make herself immediately available to evaluate the condition of the participant and intervene if necessary. We do not anticipate adverse reactions or any greater risk to be induced by our study than during daily life, however, we have developed a plan should a cannabis or non-cannabis related negative event occur. First, we always have two trained members of the research staff in the Mobile Laboratory every time they are with a participant. Should a concerning event arise, if it is an emergency, staff will be instructed to immediately call 911. Second, or in a non-emergency case, staff will call Dr. Bidwell, Dr. Bryan, and/or Dr. Hutchison (who will be on call/reachable during all scheduled appointments) to resolve the situation. First, it will be determined if the situation can be resolved over the phone. If not, the PI or Co-I will immediately drive to the Mobile Laboratory for further assessment of the participant and situation. The participant will be given the option of withdrawing from the study and medical or mental health referrals will be made as appropriate and as determined by the clinically trained Senior Investigators. Importantly, Mobile lab staff are First Aid trained and the PI Bidwell and Co-I Hutchison are both licensed clinical psychologists.

Another potential risk that the study team will be prepared to manage is participant endorsement of thoughts of suicide on the BDI. The BDI is a measure of depression symptomatology that will be included on the baseline surveys. Item number 9 from the BDI inquiries about "suicidal thoughts or wishes" that participants may or may not be experiencing. REDCap, the online survey system that we will use to administer our inventories for this project, has a feature that allows researchers to receive an email alert if a participant responds to particular items with a specific response. In order to ensure the safety of our participants, we will program the survey to alert the study coordinator, who will then immediately notify the PI or co-I Hutchison (both licensed clinical psychologists), if a participant responds to item 9 from the BDI with any response other than, "I don't have any thoughts about killing myself or "I have thoughts of killing myself, but I would not carry them out". If a participant was to respond to item 9 from the BDI with a different response (i.e., "I would like to kill myself;" or "I would kill myself if I had the chance"), Drs. Bidwell or Hutchison would immediately assess the participant for imminent suicide risk and provide him/her with a list of psychological services referral contacts. After the participant has been assessed for risk, the study coordinator will use the CU CHANGE lab's previously IRB approved 'Suicide Ideation Protocol' to connect the participant with an appropriate referral resource (i.e., 911 if in imminent danger, Boulder County Mental Health Center (BCMHC) if the participant is a community

member, or Wardenburg Health Center and/or BCMHC if the participant is a CU Boulder student, staff, or faculty member). The study coordinator will immediately follow up with the PI to ensure that all of the necessary measures had been taken to protect the safety of the participant. During this meeting the PI and study coordinator, in consultation with Dr. Hutchison, will determine whether or not it is safe for the participant to continue his/her involvement in the study. If it is determined that the participant is at imminent risk and should not continue participating in the study, the study coordinator will contact the participant and explain that for his/her safety, the research team does not feel that it is safe for him/her to continue participating in the study. The study coordinator will also answer any questions that the participant may have about this decision.

Risks Pertaining to Loss of Confidentiality and Privacy

We intend to mitigate risks as much as possible by collecting the minimum amount of identifying information from participants necessary to conduct our study. Participants' information will be coded with a randomly generated number, and the document linking their number with their contact information will be stored on a password protected server that is only accessible by members of the research staff.

All study computers are password protected and housed in the PI's lab space at the CINC, which are kept locked unless researchers or students are currently using the space. Further, there is no identifying information contained on the laptops. All identifying information (e.g., consent forms, contact information) is kept separate and secure from the data files and never on the same laptop.

XVIII. POTENTIAL BENEFITS

There is no direct benefit to participants for their participation; however, all participants will have the opportunity to examine their own cannabis use in the context of completing the measures. The minimal costs associated with participation in this research seem reasonable in relation to the scientific importance of gaining insight into the health-related implications of cannabis use, particularly given the timely nature of this study and the recent legislation regarding cannabis.

XIX. PROVISIONS TO MONITOR THE DATA FOR THE SAFETY OF PARTICIPANTS

The project manager will monitor and report to the PI on adherence to the protocol. He/she will assess adherence via periodic observation of the appointments, visual inspection of the completeness of data collection, and verification of follow-up information collected from participants (to ensure they have agreed to be contacted and there are no safety concerns that arise). He/she will give bi-weekly reports to the PI. The PI will be in daily contact with the research assistants running the study and will be informed immediately of any adverse event. Consistent with IRB policy, the project manager will use the Reportable Event eForm and/or the Deviation eForm in eRA to report all adverse events consistent with those listed under points 19.1 (adverse events) and 19.2 (deviations) in the CU Boulder IRB policy procedures document: http://www.colorado.edu/VCResearch/integrity/humanresearch/SOP_TOC.html.

For any other problem or event requiring reporting to the IRB, the PI or designee will submit to the IRB a Reportable Event or Deviation in eRA as soon as possible, but no later than 10 working days from notification of event.

XX. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

To ensure participants' confidentiality, all data will be identified with a unique research subject identifier in a randomized, confidential manner. This system is operated by the research team member who can only access the program by using a login name and password. The list linking the numerical

identifier to the participant's identifying information will be maintained separate and secure from the data and will be destroyed at study closure. The data files themselves will be maintained in the CINC at the University of Colorado, and will be identified only by the numeric identifier. Only staff cleared on a specific project can view data collected on that given project.

Fully informed consent will be sought to ensure that participants are aware of any possible risks. Participation in the research is completely voluntary, as is answering each particular question in the screening and in all of the measures.

XXI. MEDICAL CARE AND COMPENSATION FOR INJURY

Participants will be informed to contact Dr. Bidwell immediately by phone (303-735-5383) should they feel that they have been harmed while participating in this study. They will be told that the cost for any treatment will be billed to them or their medical or hospital insurance. Information regarding compensation for injury is included in the informed consent document.

XXII. COST TO PARTICIPANTS

Participants will be responsible for paying for the cannabis that they choose and purchase. We estimate the approximate cost of edibles for 2 weeks to be $90, depending in part on what type and how much each participant chooses to use. Parking is free at the CINC.

XXIII. DRUG ADMINISTRATION

Not Applicable.

XXIV. INVESTIGATIONAL DEVICES

Not applicable.

XXV. MULTI-SITE STUDIES

Not applicable. All drug use will be self-directed.

XXVI. SHARING OF RESULTS WITH PARTICIPANTS

There are no plans to share results of the study with participants.

Table 4.	Schedule of Evaluations						
Assessment:	**Screening:**	**Baseline Visit 1:**	**Daily:**	**2-Week Visit 2:**			**Monthly:**
	Phone/ Online	Enrollment, Randomization, Observation <Pre-2w SA>	Follow-up Surveys	Observation <Pre-0h SA>	<Post-1h SA>	<Post-2h SA>	Follow-up Surveys
	(d: -14) (w: -2)	(d: 1) (w: 1)	(d: 2-15) (w: 1-2)	(d: 16) (w: 2)	(d: 16) (w: 2)	(d: 16) (w: 2)	(d: 30+) (w: 4+) (m: 1-6)
Time point		In-Person (1d) 1 time point	Online (14d) 14 time points	In-Person (1d) 3 time points			Online (6m) 6 time points
Eligibility Screening Form/Scheduling (Inclusion/Exclusion Criteria Table 2)	X	X					
Physician Review (If needed for eligibility or safety concerns)	X						
Informed Consent Form/Enrollment		X					
Breathalyzer/Alcohol Content Test		X		X			
Blood Pressure (BP)		X		X	X	X	
Physiological Weight Scale		X		X			
Stadiometer (Height)		X					
Medical History & Prescribed Medication Use		X		X*			X*
Urine Analysis (Pregnancy & Toxicology)		X					
Demographics (D)		X					
Alcohol Use History (AUH)		X					
Alcohol Use Disorder Identification test (AUDIT)		X					
Marijuana Purchasing Task (MPT)		X		X			
Beck Depression Inventory-II (BDI-II)		X					
Beck Anxiety Scale (BAI)		X					

ADHD Self-Report Scale (ASRS)		X					
Pain Intensity (PIT7)		X		X			X
Pain Interference (PIF7)		X		X			X
Marijuana Dependence Scale (MDS)		X		X			X
Marijuana users Cohort (MUHC)		X*					
Impact of Marijuana on Pain (IMP)		X		X*			X*
Health Related Questionnaire (HRQL/SF-12)		X		X			X
*Time Line Follow Back (TLFB)		X		X			X
Pittsburg Sleep Quality Index (PSQI)		X		X			X
*Roland Morris Disability Questionnaire (RMDQ)		X		X			X
Depression Anxiety Stress Scale (DASS)		X		X			X
Self-Rated Diet (SRD)		X		X			X
Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog)		X		X			X
Current Opioid Misuse Measure (COMM)		X		X			X
The Drug Effects Questionnaire (DEQ)				X	X	X	
The Addiction Research Center Inventory (M-Scale)				X	X	X	
Heart Rate (HR)		X		X	X	X	
Venous Blood Draw (BD)		X		X	X	X	
Pain Intensity-current (PITc)		X		X	X	X	X
*Pain Interference-current (PIFc)		X		X			X
Motor/Movement Battery (MB)		X		X	X	X	
International Shopping List Test (ISLT)		X		X	X	X	
Neurocognitive Toolbox Battery (NCB)		X		X	X	X	
Marijuana Craving Questionnaire (MCQ)		X		X	X	X	
Alcohol Craving Questionnaire (ACQ)		X		X	X	X	
*Profile of Mood States (POMS)		X		X	X	X	
Perceived Stress Scale (PSS)		X		X			X
Stanford Leisure-Time Activity Categorical Item (L-Cat)		X		X			X
Patient Global Impression of Change (PGIC)				X			X

Daily Questions Survey (DQS) (Daily report of cannabis use, pain, mood, and sleep)			**X**				
Approximate Assessment Duration (includes 5-10 min breaks every 30 mins)	**10 min**	**2 hour**	**2 min**	**75 min**	**45 min**	**60 min**	**15 min**

Key: d=days; w=weeks; m=months; h=hour, min=minute; SA=Self-Administration, *=use of a modified measure

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